

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059106 A1

(51) International Patent Classification⁷: C07D 401/04, 401/14, 407/14, 409/14, A61K 31/445, 31/44, 31/495, A61P 29/00, 35/00, 37/00

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(21) International Application Number: PCT/US01/50401

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(22) International Filing Date:
21 December 2001 (21.12.2001)

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

Published:

(26) Publication Language: English

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(30) Priority Data:
60/258,372 27 December 2000 (27.12.2000) US
09/972,487 5 October 2001 (05.10.2001) US

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

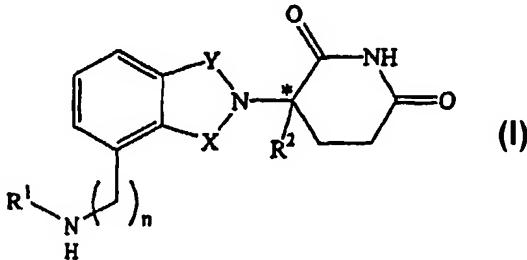
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(54) Title: ISOINDOLE-IMIDE COMPOUNDS, COMPOSITIONS, AND USES THEREOF

WO 02/059106 A1



(57) Abstract: The invention relates to isoindole-imide compounds and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixtures of stereoisomers thereof, pharmaceutical compositions comprising these isoindole-imide compounds, and methods for reducing the level of cytokines and their precursors in mammals. In particular, the invention pertains to isoindole-imide compounds that are potent inhibitors of the production of the TNF- α in mammals. The isoindole-imides described herein are useful for treating or preventing diseases or disorders in mammals, for example, cancers, such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; osteoporosis; and genetic, inflammatory, allergic; and autoimmune diseases.

Atty Docket#: 9516-078
Serial #: 10/693,722
Reference: A94

ISOINDOLE-IMIDE COMPOUNDS, COMPOSITIONS, AND USES THEREOF

This application is a continuation-in-part of United States Application No. 09/972,487 filed October 5, 2001, which claims the benefit of U.S. Provisional Application No. 60/258,372, filed December 27, 2000, and which applications are hereby expressly incorporated by reference herein.

1. Field of The Invention

The invention encompasses novel compounds including compounds having an isoindole-imide moiety, pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixtures of stereoisomers thereof, pharmaceutical compositions of these compounds, and methods of using these compounds and compositions in mammals for treatment or prevention of diseases.

15

2. Introduction

The present invention relates to isoindole-imide compounds and pharmaceutically acceptable salts, hydrates, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof; pharmaceutical compositions comprising these isoindole-imide compounds; and methods for reducing the level of cytokines and their precursors in mammals. In particular, the invention includes isoindole-imide compounds that have one or more of the following activities: modulation of the production of TNF- α ; modulation of the production of IL-1 β ; stimulation of the production of IL-10; or stimulation of the production T-cells.

The isoindole-imides described herein are useful for treating or preventing diseases or disorders in mammals, for example, cancers, such as solid tumors and blood-born tumors. Specific examples of cancers treatable or preventable by compounds of the invention include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are particularly useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias.

35

The compounds of the invention are also useful to treat or prevent heart disease, such as congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

- 5 The compounds of the invention can also be used to treat or prevent viral, genetic, inflammatory, allergic, and autoimmune diseases. For example, the compounds are useful to treat or prevent diseases including, but not limited to, HIV; hepatitis; adult respiratory distress syndrome; bone-resorption diseases; chronic pulmonary inflammatory diseases; dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; 10 cachexia; graft rejection including graft versus host disease; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; ENL in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.
- 15 The compounds of the invention are also useful for treating or preventing bacterial infections or the symptoms of bacterial infections including, but not limited to, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

3. Background of The Invention

- 20 Tumor necrosis factor alpha, (TNF- α) is a cytokine that is released primarily by mono-nuclear phagocytes in response to immunostimulators. TNF- α is capable of enhancing most cellular processes, such as differentiation, recruitment, proliferation, and proteolytic degradation. At low levels, TNF- α confers protection against infective agents, tumors, and tissue damage. But TNF- α also has role in many disease processes. When 25 administered to mammals or humans, TNF- α causes or aggravates inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Enhanced or unregulated TNF- α production has been implicated in a number of diseases and medical conditions, for example, cancers, such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; 30 and viral, genetic, inflammatory, allergic, and autoimmune diseases.

The interleukins are a subclass of the cytokine family and possess a wide spectrum of biological activities including involvement in cell activation, cell differentiation, cell proliferation, and cell-to-cell interactions. Interleukin 1 beta (IL-1 β) and interleukin 10 (IL-10), in combination with other cytokines, play a central role in mediating inflammatory

processes and IL-1 β has been implicated as both a growth factor and growth suppressor in certain tumor cells.

T-cells are a class of white blood cells that play an important role in the immune response, and help protect the body from viral and bacterial infections. Diminished T-cell 5 levels strongly contribute to the inability of HIV patients to combat infections, and abnormally low T-cell levels are prominent in a number of other immune deficiency syndromes, including DiGeorge Syndrome, and in certain forms of cancer, such as T-cell lymphoma.

Cancer is a particularly devastating disease, and increase in blood TNF- α levels are 10 implicated in the risk of and the spreading of cancer. Normally, in healthy subjects, cancer cells fail to survive in the circulatory system, one of the reasons being that the lining of blood vessels acts as a barrier to tumor-cell extravasation. But increased levels of cytokines, have been shown to substantially increase the adhesion of cancer cells to endothelium *in vitro*. One explanation is that cytokines, such as TNF- α stimulate the 15 biosynthesis and expression of a cell surface receptors called ELAM-1 (endothelial leukocyte adhesion molecule). ELAM-1 is a member of a family of calcium-dependent cell adhesion receptors, known as LEC-CAMs, which includes LECAM-1 and GMP-140. During an inflammatory response, ELAM-1 on endothelial cells functions as a "homing receptor" for leukocytes. Recently, ELAM-1 on endothelial cells was shown to mediate the 20 increased adhesion of colon cancer cells to endothelium treated with cytokines (Rice *et al.*, 1989, *Science* 246:1303-1306). It has been suggested that an uncontrolled synthesis of IL-1 β in leukemia blast cells is thought to result in the production of factors which promote proliferation of these malignant cells (Hestdal *et al.*, 1992, *Blood* 80: 2486-94). In addition to this, IL-1 β , in combination with other cytokines, appears to stimulate the growth of 25 human gastric and thyroid carcinoma cells (Ito *et. al.*, 1993, *Cancer Research* 53: 4102-6).

Inflammatory diseases such as arthritis, related arthritic conditions (e.g. osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, sepsis, psoriasis, and chronic inflammatory pulmonary diseases are also prevalent and problematic ailments. Both TNF- α and IL-1 β play central roles in the inflammatory response and the administration of 30 their antagonists block chronic and acute responses in animal models of inflammatory disease. Conversely, IL-10 is an anti-inflammatory cytokine and is responsible for down-regulating inflammatory responses and as such possesses anti-inflammatory ability, including the suppression of production of proinflammatory cytokines such as TNF- α and IL-1 β .

Heart disease has caused wide-spread death and debilitation. TNF- α has been implicated in a broad variety of cardiac pathophysiological conditions, such as septic shock, acute viral myocarditis, cardiac allograft rejection, myocardial infarction, and congestive heart failure (see e.g., Steadman *et al.*, 1988, *IEEE Trans. Biomed. Eng.* 35:264-272; Tracey *et al.*, 1986, *Science Wash. DC* 234:470-474; for a review see Ferrari, 1998, *Cardiovascular Research* 37:554-559). In one study, it was found that protective TNF- α binding proteins are downregulated in the hearts of patients with advanced congestive heart failure. During the study it was found that a large percentage of the diseased hearts analyzed had elevated TNF- α levels. The authors noted that the results support the proposition that the heart itself is a target of TNF- α and that myocardial TNF- α production may be a maladaptive mechanism that contributes to progressive heart failure (Torre-Amione *et al.*, 1996, *Circulation* 93:704-711). In other studies, it has been demonstrated *in-vitro* and *in-vivo* (feline) that TNF- α is produced in the myocardium portion of the heart upon endotoxin stimulation. These studies provide compelling evidence indicating that a pathogenic level of biologically active TNF- α may be produced in the heart during endotoxin-mediated septic shock. And that such local concentrations of TNF- α may be the primary instigator of myocardial-function depression during systemic sepsis (Kapadia *et al.*, 1995, *J. Clin. Invest.* 96:1042-1052). Thus, inhibitors of TNF- α activity may prevent its deleterious effects on the heart. For example, it has been demonstrated that soluble TNF-binding proteins modulate the negative inotropic effects of TNF- α *in vitro* in isolated contracting cardiac myocytes (Kapadia *et al.*, 1995, *Am. J. Physiol.* 268:H517-H525).

Enhanced or unregulated TNF- α production has been implicated in viral, genetic, inflammatory, allergic, and autoimmune diseases, for example, HIV; hepatitis; adult respiratory distress syndrome; bone-resorption diseases; chronic pulmonary inflammatory diseases; dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis, Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; ENL in leprosy; radiation damage; asthma; and hyperoxic alveolar injury. For discussions see Tracey *et al.*, 1987, *Nature* 330:662-664 and Hinshaw *et al.*, 1990, *Circ. Shock* 30:279-292 (endotoxic shock); Dezube *et al.*, 1990, *Lancet*, 335:662 (cachexia); Millar *et al.*, 1989, *Lancet* 2:712-714 and Ferrai-Baliviera *et al.*, 1989, *Arch. Surg.* 124:1400-1405 (adult respiratory distress syndrome); Bertolini *et al.*, 1986, *Nature* 319:516-518, Johnson *et al.*, 1989, *Endocrinology* 124:1424-1427, Holler *et al.*, 1990, *Blood*

75:1011-1016, and Grau *et al.*, 1989, *N. Engl. J. Med.* 320:1586-1591 (bone resorption diseases); Pignet *et al.*, 1990, *Nature*, 344:245-247, Bissonnette *et al.*, 1989, *Inflammation* 13:329-339 and Baughman *et al.*, 1990, *J. Lab. Clin. Med.* 115:36-42 (chronic pulmonary inflammatory diseases); Elliot *et al.*, 1995, *Int. J. Pharmac.* 17:141-145 (rheumatoid arthritis); von Dullemen *et al.*, 1995, *Gastroenterology*, 109:129-135 (Crohn's disease); Duh *et al.*, 1989, *Proc. Nat. Acad. Sci.* 86:5974-5978, Poll *et al.*, 1990, *Proc. Nat. Acad. Sci.* 87:782-785, Monto *et al.*, 1990, *Blood* 79:2670, Clouse *et al.*, 1989, *J. Immunol.* 142, 431-438, Poll *et al.*, 1992, *AIDS Res. Hum. Retrovirus*, 191-197, Poli *et al.* 1990, *Proc. Natl. Acad. Sci.* 87:782-784, Folks *et al.*, 1989, *PNAS* 86:2365-2368 (HIV and opportunistic infections resulting from HIV).

- Pharmaceutical compounds that can block the activity or inhibit the production of certain cytokines, including TNF- α and IL-1 β , may be beneficial therapeutics. Many small-molecule inhibitors have demonstrated an ability to treat or prevent inflammatory diseases implicated by TNF- α (for a review see Lowe, 1998 *Exp. Opin. Ther. Patents* 8:1309-1332).
- 15 In addition, pharmaceutical compounds that can stimulate the activity or increase the production of certain cytokines, including IL-10, and immune response factors such as T-cells, may be beneficial therapeutics.

Thalidomide is an emerging immunotherapeutic agent and, in addition to utility in treating a variety of inflammatory disorders, it is projected to be useful in treating cancers (see e.g., Marriott *et al.*, 1999, *Immunology Today* 20:537-540). Thalidomide has been shown to inhibit production of both TNF- α and IL-1 β while simultaneously increasing the production of IL-10 and T-cells, and has been tested against a variety of autoimmune and inflammatory diseases, see e.g., Gutierrez-Rodriguez, 1984, *Arth. and Rheum* 27:1118; *The Physician's Desk Reference*, 54th edition, 911-916, Medical Economics Company (2000).

20 25 Thalidomide's teratogenic properties, however, have limited its use and driven efforts to discover analogs or derivatives with reduced toxicity and improved therapeutic activity. The design of thalidomide analogs and derivatives attempts to maintain/enhance activity while subverting toxicity (for a discussion of some recent advances in TNF- α inhibitors structurally related to thalidomide see Marriott, 1997, *Exp. Opin. Invest. Drugs* 6:1105-1108). For example, the following references have disclosed alternatives to thalidomide as inhibitors of TNF- α production: U.S. Patent Nos. 5,385,901; 5,635,517; and 5,798,368 and PCT International Application WO 98/54170. Despite these disclosures, there remains a need for non-toxic and high-potency compounds that treat or prevent cancer, inflammatory disorders, and autoimmune diseases.

Citation or identification of any reference in Section 3 of this application is not an admission that such reference is available as prior art to the present invention.

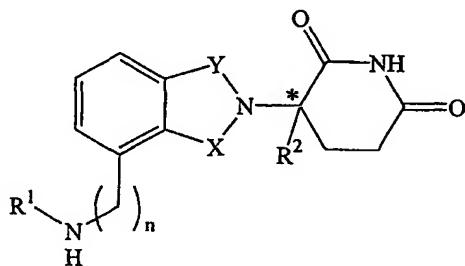
4. Summary of the Invention

5 The invention encompasses novel isoindole-imide compounds and compositions thereof that are useful to treat or prevent diseases in mammals, including humans. The invention further encompasses the use of these compounds for treating or preventing diseases or disorders including, but not limited to, cancer; viral, genetic, inflammatory, allergic, and autoimmune diseases; and bacterial infections. The compounds of the
 10 invention are particularly useful to treat or prevent diseases caused or aggravated by excessive or unregulated levels of TNF- α , or IL-1 β ; or diminished or unregulated levels of IL-10 or T-cells.

In one embodiment, the invention relates to compounds encompassed by Formula I :

15

20

**I**

wherein:

25 one of X and Y is C=O and the other is CH₂ or C=O;

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³, C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³,
 30 C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

R² is H, F, benzyl, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, or (C₂-C₈)alkynyl;

R³ and R^{3'} are independently (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl,
 35 (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl,

(C₀—C₄)alkyl—(C₂—C₅)heteroaryl, (C₀—C₈)alkyl—N(R⁶)₂, (C₁—C₈)alkyl—OR⁵,
 (C₁—C₈)alkyl—C(O)OR⁵, (C₁—C₈)alkyl—O(CO)R⁵, or C(O)OR⁵;

- R⁴ is (C₁—C₈)alkyl, (C₂—C₈)alkenyl, (C₂—C₈)alkynyl, (C₁—C₄)alkyl—OR⁵, benzyl, aryl,
 5 (C₀—C₄)alkyl—(C₁—C₆)heterocycloalkyl, or (C₀—C₄)alkyl—(C₂—C₅)heteroaryl;
 R⁵ is (C₁—C₈)alkyl, (C₂—C₈)alkenyl, (C₂—C₈)alkynyl, benzyl, aryl, or (C₂—C₅)heteroaryl;
 each occurrence of R⁶ is independently H, (C₁—C₈)alkyl, (C₂—C₈)alkenyl, (C₂—C₈)alkynyl,
 10 benzyl, aryl, (C₂—C₅)heteroaryl, or (C₀—C₈)alkyl—C(O)O—R⁵ or the R⁶ groups can join to
 form a heterocycloalkyl group;

n is 0 or 1; and

- 15 * represents, in formula I and in the following formulas of the invention, a chiral-carbon center; with the proviso that when n is 0 then R¹ is not H.

In a separate embodiment, the compounds of the invention include compounds of formula I, wherein when n is 0 then R¹ is (C₃—C₇)cycloalkyl, (C₂—C₈)alkenyl, (C₂—C₈)alkynyl, benzyl, aryl, (C₀—C₄)alkyl—(C₁—C₆)heterocycloalkyl,
 20 (C₀—C₄)alkyl—(C₂—C₅)heteroaryl, C(O)R³, C(O)OR⁴, (C₁—C₈)alkyl—N(R⁶)₂,
 (C₁—C₈)alkyl—OR⁵, (C₁—C₈)alkyl—C(O)OR⁵, C(S)NHR³, or (C₁—C₈)alkyl—O(CO)R⁵;

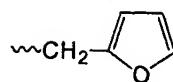
R² is H or (C₁—C₈)alkyl; and

- 25 R³ is (C₁—C₈)alkyl, (C₃—C₇)cycloalkyl, (C₂—C₈)alkenyl, (C₂—C₈)alkynyl, benzyl, aryl,
 (C₀—C₄)alkyl—(C₁—C₆)heterocycloalkyl, (C₀—C₄)alkyl—(C₂—C₅)heteroaryl,
 (C₅—C₈)alkyl—N(R⁶)₂; (C₀—C₈)alkyl—NH—C(O)O—R⁵; (C₁—C₈)alkyl—OR⁵,
 (C₁—C₈)alkyl—C(O)OR⁵, (C₁—C₈)alkyl—O(CO)R⁵, or C(O)OR⁵; and the other variables are as
 described above.

- 30 In another embodiment of the compounds of formula I, R² is H or (C₁—C₄)alkyl.

In still another embodiment of the compounds of formula I, R¹ is (C₁—C₈)alkyl or
 benzyl.

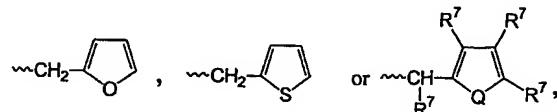
In yet another embodiment of the compounds of formula I, R¹ is H, (C₁—C₈)alkyl,
 benzyl, CH₂OCH₃, CH₂CH₂OCH₃, or



5

In another embodiment of the compounds of formula I, R¹ is

10



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen,
15 (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl,
(C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or
C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl
ring.

In still another embodiment of the compounds of formula I, R¹ is C(O)R³ or
20 C(O)OR⁴.

In another embodiment of the compounds of formula I, R³ is

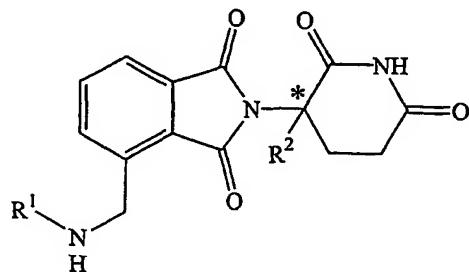
(C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₁-C₈)alkyl, aryl, or (C₀-C₄)alkyl-OR⁵.

In yet another embodiment of the compounds of formula I, heteroaryl is pyridyl,
furyl, or thienyl.

25 In another embodiment of the compounds of formula I, the H of C(O)NHC(O) can
be replaced with (C₁-C₄)alkyl, aryl, or benzyl.

In another embodiment, the invention encompasses compounds of Formula II:

30



35

II

wherein:

R¹ is H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl,
 5 (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, C(O)R³, C(S)R³,
 C(O)OR⁴, (C₁–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, C(O)NHR³,
 C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁–C₈)alkyl–O(CO)R⁵;

R² is H or (C₁–C₈)alkyl;

10 R³ and R^{3'} are independently (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl,
 (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl,
 (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵,
 (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;

15 R⁴ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, (C₁–C₄)alkyl–OR⁵, benzyl, aryl,
 (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, or (C₀–C₄)alkyl–(C₂–C₅)heteroaryl;

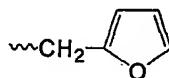
20 R⁵ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, or (C₂–C₅)heteroaryl;

each occurrence of R⁶ is independently H, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl,
 benzyl, aryl, (C₂–C₅)heteroaryl, or (C₀–C₈)alkyl–C(O)O–R⁵ or the R⁶ groups can join to
 form a heterocycloalkyl group; and

25 the * represents a chiral-carbon center.

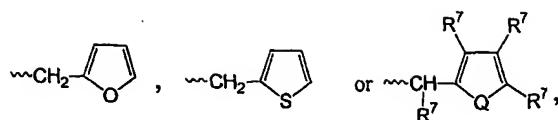
In another embodiment of the compounds of formula II, R¹ is H, (C₁–C₄)alkyl,
 CH₂OCH₃, CH₂CH₂OCH₃, or

30



In yet another embodiment of the compounds of formula II, R¹ is

35



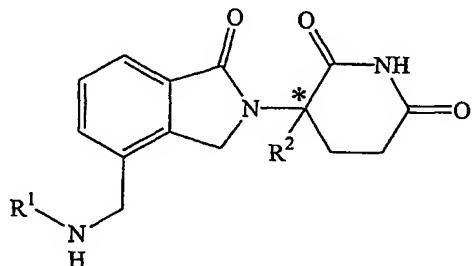
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- wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl,
- 10 (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

In still another embodiment of the compounds of formula II, R¹ is C(O)R³ or C(O)OR⁴.

- 15 In a further embodiment, the invention encompasses compounds of Formula III:

20

**III**

wherein:

25

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³, C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³, C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

30

R² is H or (C₁-C₈)alkyl;

R³ and R^{3'} are independently is (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl,

35

(C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;

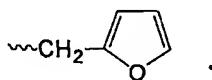
R⁴ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, (C₁–C₄)alkyl–OR⁵, benzyl, aryl,
5 (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, or (C₀–C₄)alkyl–(C₂–C₅)heteroaryl;

R⁵ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, or (C₂–C₅)heteroaryl;

each occurrence of R⁶ is independently H, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl,
10 benzyl, aryl, (C₂–C₅)heteroaryl, or (C₀–C₈)alkyl–C(O)O–R⁵ or the R⁶ groups can join to
form a heterocycloalkyl group; and

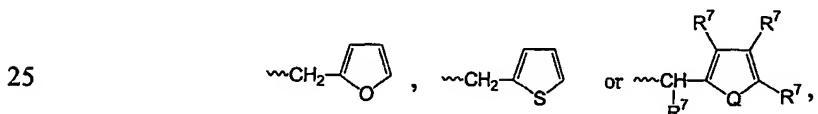
the * represents a chiral-carbon center.

In yet another embodiment of the compounds of formula III, R¹ is H, (C₁–C₄)alkyl,
15 CH₂OCH₃, CH₂CH₂OCH₃, or



20

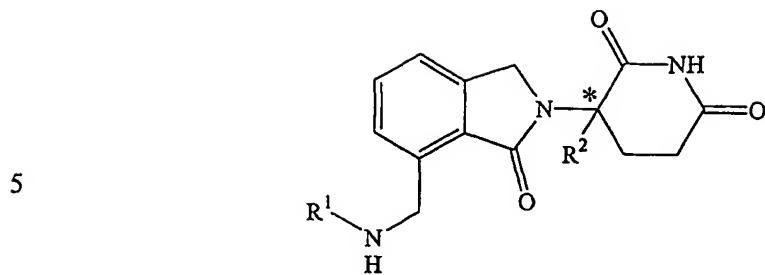
In another embodiment of the compounds of formula III, R¹ is



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, halogen, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl,
30 (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring..

In still another embodiment of the compounds of formula III, R¹ is C(O)R³ or C(O)OR⁴.

35 In a further embodiment still, the invention encompasses compounds of Formula IV:



wherein:

10

R^1 is H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^3'$, $C(S)NR^3R^3'$ or (C_1-C_8) alkyl- $O(CO)R^5$;

15

R^2 is H or (C_1-C_8) alkyl;

R^3 and R^3' are independently (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl,

20 (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_0-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$;

R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl- OR^5 , benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, or (C_0-C_4) alkyl- (C_2-C_5) heteroaryl;

25

R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl;

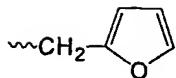
each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl- $C(O)O-R^5$ or the R^6 groups can join to

30 form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

In another embodiment of the compounds of formula IV, R^1 is H, (C_1-C_4) alkyl, CH_2OCH_3 , $CH_2CH_2OCH_3$, or

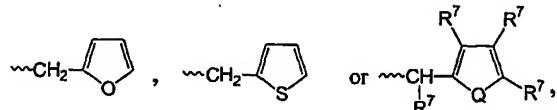
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5

In yet another embodiment of the compounds of formula IV, R¹ is

10

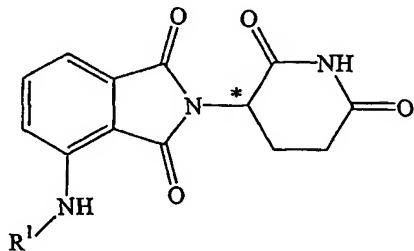


wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen,
15 (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl,
(C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or
C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl
ring.

In still another embodiment of the compounds of formula IV, R¹ is C(O)R³ or
20 C(O)OR⁴.

In yet another embodiment, the invention encompasses compounds of Formula V:

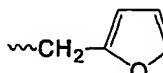
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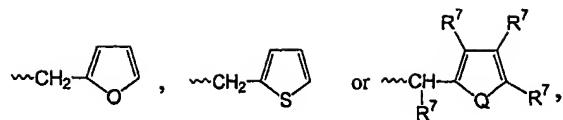


V

30 wherein:

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl,
(C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³,
C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³,
35 C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

- R³ and R³ are independently (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵,
- 5 (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;
- R⁴ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, (C₁–C₄)alkyl–OR⁵, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, or (C₀–C₄)alkyl–(C₂–C₅)heteroaryl;
- 10 R⁵ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, or (C₂–C₅)heteroaryl; each occurrence of R⁶ is independently H, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₂–C₅)heteroaryl, or (C₀–C₈)alkyl–C(O)O–R⁵ or the R⁶ groups can join to form a heterocycloalkyl group; and
- 15 the * represents a chiral-carbon center.
- In a separate embodiment of compounds of formula V, R¹ is (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, C(O)R³, C(O)OR⁴, (C₁–C₈)alkyl–N(R⁶)₂,
- 20 (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, or (C₁–C₈)alkyl–O(CO)R⁵; and
- R³ is (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₃–C₈)alkyl–N(R⁶)₂; (C₀–C₈)alkyl–NH–C(O)O–R⁵; (C₁–C₈)alkyl–OR⁵,
- 25 (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵; and the other variables have the definitions above.
- In another embodiment of the compounds of formula V, R¹ is (C₁–C₈)alkyl or benzyl, CH₂OCH₃, CH₂CH₂OCH₃, or
- 30
- ~~CH₂—
- In another embodiment of the compounds of formula V, R¹ is
- 35



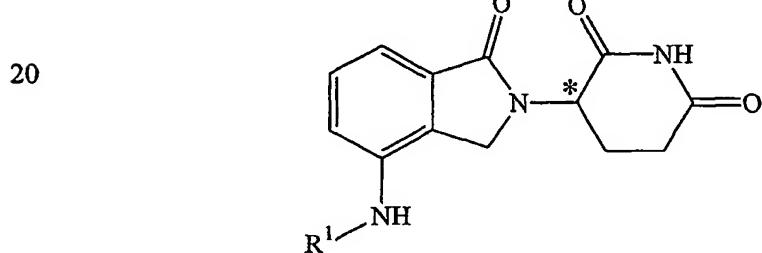
5 wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl 10 ring.

In still another embodiment of the compounds of formula V, R¹ is C(O)R³ or C(O)OR⁴.

In another embodiment of the compounds of formula V, R³ is (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₁-C₈)alkyl, aryl, or (C₀-C₄)alkyl-OR⁵.

15 In yet another embodiment of the compounds of formula V, heteroaryl is pyridyl, furyl, or thienyl.

In another embodiment, the invention further provides compounds of Formula VI:



25

wherein:

R¹ is (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(S)NHR³, or (C₁-C₈)alkyl-O(CO)R⁵;

R³ is (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl,

35

$(C_0-C_8)alkyl-N(R^6)_2$, $(C_1-C_8)alkyl-OR^5$, $(C_1-C_8)alkyl-C(O)OR^5$, $(C_1-C_8)alkyl-O(CO)R^5$, or $C(O)OR^5$;

- R^4 is $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_1-C_4)alkyl-OR^5$, benzyl, aryl,
5 $(C_0-C_4)alkyl-(C_1-C_6)heterocycloalkyl$, or $(C_0-C_4)alkyl-(C_2-C_5)heteroaryl$;

R^5 is $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, benzyl, aryl, or $(C_2-C_5)heteroaryl$;

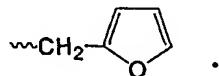
- each occurrence of R^6 is independently H, $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$,
10 benzyl, aryl, $(C_2-C_5)heteroaryl$, or $(C_0-C_8)alkyl-C(O)O-R^5$ or the R^6 groups can join to
form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

- In a separate embodiment of compounds of formula VI, R^1 is $(C_3-C_7)cycloalkyl$,
15 $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, benzyl, aryl, $(C_0-C_4)alkyl-(C_1-C_6)heterocycloalkyl$,
 $(C_0-C_4)alkyl-(C_2-C_5)heteroaryl$, $C(O)R^3$, $C(O)OR^4$, $(C_1-C_8)alkyl-N(R^6)_2$,
 $(C_1-C_8)alkyl-OR^5$, $(C_1-C_8)alkyl-C(O)OR^5$, $C(S)NHR^3$, or $(C_1-C_8)alkyl-O(CO)R^5$; and

- R^3 is $(C_1-C_8)alkyl$, $(C_3-C_7)cycloalkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, benzyl, aryl,
20 $(C_0-C_4)alkyl-(C_1-C_6)heterocycloalkyl$, $(C_0-C_4)alkyl-(C_2-C_5)heteroaryl$,
 $(C_5-C_8)alkyl-N(R^6)_2$, $(C_0-C_8)alkyl-NH-C(O)O-R^5$, $(C_1-C_8)alkyl-OR^5$,
 $(C_1-C_8)alkyl-C(O)OR^5$, $(C_1-C_8)alkyl-O(CO)R^5$, or $C(O)OR^5$; and the other variables are
defined as above.

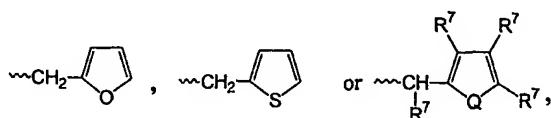
- In another embodiment of the compounds of formula VI, R^1 is $(C_1-C_8)alkyl$, benzyl,
25 CH_2OCH_3 , $CH_2CH_2OCH_3$, or



30

In another embodiment of the compounds of formula VI, R^1 is

35



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, halogen, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or 5 C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

In still another embodiment of the compounds of formula VI, R¹ is C(O)R³ or C(O)OR⁴.

In another embodiment of the compounds of formula VI, R³ is

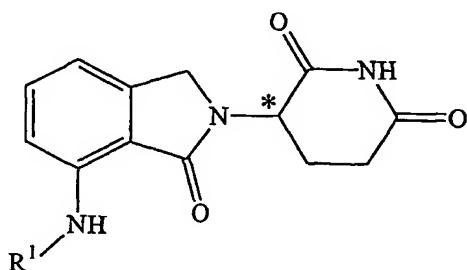
10 (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₁–C₈)alkyl, aryl, or (C₀–C₄)alkyl–OR⁵.

In yet another embodiment of the compounds of formula VI, heteroaryl is pyridyl, furyl, or thienyl. In another embodiment of the compounds of formula VI, the H of C(O)NHC(O) can be replaced with (C₁–C₄)alkyl, aryl, or benzyl.

In still another embodiment, the invention encompasses compounds of Formula VII:

15

20



VII

wherein:

- 25 R¹ is (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, C(O)R³, C(O)OR⁴, (C₁–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, C(S)NHR³, or (C₁–C₈)alkyl–O(CO)R⁵;
- 30 R³ is (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;

35

R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl- OR^5 , benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, or (C_0-C_4) alkyl- (C_2-C_5) heteroaryl;

R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl;

5

each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl- $C(O)O-R^5$ or the R^6 groups can join to form a heterocycloalkyl group; and

10 the * represents a chiral-carbon center.

In a separate embodiment of compounds of formula VII, R^1 is (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, $C(O)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, $C(S)NHR^3$, or (C_1-C_8) alkyl- $O(CO)R^5$; and

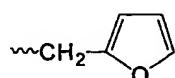
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R^3 is (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_5-C_8) alkyl- $N(R^6)_2$; (C_0-C_8) alkyl- $NH-C(O)O-R^5$; (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$; and the other variables are as

20 defined above.

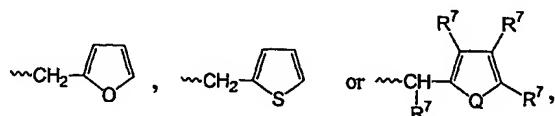
In another embodiment of the compounds of formula VII R^1 is (C_1-C_8) alkyl, benzyl, CH_2OCH_3 , $CH_2CH_2OCH_3$, or

25



In another embodiment of the compounds of formula VII, R^1 is

30



wherein Q is O or S, and each occurrence of R^7 is independently H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, halogen,

(C₀—C₄)alkyl—(C₁—C₆)heterocycloalkyl, (C₀—C₄)alkyl—(C₂—C₅)heteroaryl, (C₀—C₈)alkyl—N(R⁶)₂, (C₁—C₈)alkyl—OR⁵, (C₁—C₈)alkyl—C(O)OR⁵, (C₁—C₈)alkyl—O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

5 In still another embodiment of the compounds of formula VII, R¹ is C(O)R³ or C(O)OR⁴.

In another embodiment of the compounds of formula VII, R³ is

(C₀—C₄)alkyl—(C₂—C₅)heteroaryl, (C₁—C₈)alkyl, aryl, or (C₀—C₄)alkyl—OR⁵. In yet another embodiment of the compounds of formula VII, heteroaryl is pyridyl, furyl, or thienyl.

10 As used herein, the phrase "compounds of the invention" means, collectively, compounds falling within Formulas I, II, III, IV, V, VI, and VII and include pharmaceutically acceptable salts, hydrates, solvates, and clathrates thereof.

The compounds of the invention generally exist in solid form and can be recrystallized according to well-known methods affording high-purity crystals, preferably, 15 in greater than 95% purity, more preferably, in greater than 98% purity. Narrow melting-point range is an indication of purity, thus, compounds of the invention generally have a melting point within a range of 3 °C to 4 °C, more preferably, within a range of 2 °C.

The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, 20 geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding enantiomers and stereoisomers, that is, both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, *e.g.*, racemates.

25 A compound of the invention is considered optically active or enantiomerically pure (*i.e.*, substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically enriched form when the compound has an 30 enantiomeric excess of greater than about 1% ee, preferably greater than about 5% ee, more preferably, greater than about 10% ee with respect to a particular chiral center. As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically pure, enantiomerically enriched, and racemic mixtures of 35 compounds of Formulas I through VII.

Enantiomeric and stereoisomeric mixtures of compounds of the invention can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a 5 chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

The invention further encompasses prodrugs of compounds falling within Formulas I, II, III, IV, V, VI, and VII. The term "prodrug" refers to a compound that, following 10 administration in a mammal, converts, via a biotransformation, into a compound falling within Formulas I, II, III, IV, V, VI, and VII *in vivo*. Prodrugs of compounds falling within Formulas I, II, III, IV, V, VI, and VII can be synthesized using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Chemistry, Fifth Ed., Vol. 1, pp. 172-178, 949-982 (1995).

15 The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

In another embodiment, the present invention further provides pharmaceutical 20 compositions comprising a therapeutically effective or a prophylactically effective amount of one or more compounds of the invention and a pharmaceutically acceptable vehicle or carrier. A pharmaceutically acceptable vehicle or carrier can comprise an excipient, diluent, or a mixture thereof. The term "therapeutically effective amount" means the amount of a compound of the invention that will elicit the biological or medical response in a mammal 25 that is being that is being treated by the veterinarian or clinician. The term "prophylactically effective" means the amount of a compound of the invention that will prevent or inhibit affliction or mitigate affliction of a mammal with a medical condition that a veterinarian or clinician is trying to prevent, inhibit, or mitigate.

In another embodiment, the invention concerns a method of modulating the 30 production or lowering the levels of TNF- α in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In yet another embodiment, the invention concerns a method of modulating the production or lowering the levels of IL-1 β in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In a further embodiment, the invention concerns a method of modulating the production or increasing the levels of IL-10 in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In still another embodiment, the invention concerns a method of modulating the 5 production or increasing the levels of T-cells in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In still another embodiment, the invention concerns a method of treating or preventing cancer in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention. The compounds of the invention can be 10 used to treat or prevent any cancer, for example, solid tumors and blood-born tumors.

Specific examples of cancers treatable or preventable by compounds of the invention include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal 15 passages; and AIDS-related cancers. The compounds are particularly useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias. The compounds of the invention can be used for treating or preventing either primary or metastatic tumors.

20 In yet one more embodiment, the invention provides methods of treating or preventing cancer in a mammal, comprising administering to a mammal in need thereof, a therapeutically effective amount of a compound of the invention and another cancer chemotherapeutic agent.

In yet another embodiment, the invention concerns a method of treating or 25 preventing inflammatory disorders in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention. The compounds of the invention are especially effective to treat or prevent inflammatory diseases related to the up-regulation of TNF- α , including, but not limited to, arthritic conditions, such as, rheumatoid arthritis, and osteoarthritis; rheumatoid spondylitis; psoriasis; post ischemic perfusion 30 injury; inflammatory bowel disease; and chronic inflammatory pulmonary disease.

In one more embodiment still, the invention provides methods of treating or preventing inflammatory disorders in a mammal, comprising administering to a mammal in need thereof, a therapeutically effective amount of a compound of the invention and another anti-inflammatory agent.

In a further embodiment, the invention concerns a method of treating or preventing heart disease in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention. For example, the compounds of the invention can be used to treat or prevent congestive heart failure, cardiomyopathy,
5 pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

In an additional embodiment, the invention concerns a method of treating or preventing osteoporosis in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention.
10 In a further embodiment, the invention relates to a method of treating or preventing viral, genetic, inflammatory, allergic, and autoimmune diseases. For example, the compounds are useful to treat or prevent diseases including, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock,
15 hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, asthma, or hyperoxic alveolar injury in a mammal comprising administering to said mammal a
20 therapeutically effective amount of a compound of the invention.

In still another embodiment, the invention concerns a method of treating or preventing malaria, mycobacterial infection, or an opportunistic infection resulting from HIV in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention.
25 In still one more embodiment, the invention relates to treating or preventing mammals having more than one of the conditions treatable by a compound of the invention.

In the above embodiments, it is preferable that the mammal be in need of the treatment or prevention, that is, the mammal is actually suffering from a medical condition or at risk of a medical condition for which a compound of the invention can provide
30 treatment or prevention. However, the compounds of the invention can also be administered to test animals that do not necessarily require such treatment or prevention.

In a further embodiment, the invention encompasses a method of modulating the production or lowering the levels of TNF- α in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or
35 tissue.

In yet another embodiment, the invention encompasses a method of modulating the production or lowering the levels of IL-1 β in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or tissue.

5 In still another embodiment, the invention encompasses a method of modulating the production or lowering the levels of IL-10 in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or tissue.

10 In still another embodiment, the invention encompasses a method of modulating the production or lowering the levels of T-cells in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or tissue.

15 In these embodiments, the term "effective amount" means the amount of the compound that will induce the biological response sought by the researcher, veterinarian, physician, or clinician. It should be understood that the cell can be in a cell culture or a tissue culture (*in vitro*) or in an organism (*in vivo*) including a human.

The present invention may be understood by reference to the detailed description and examples that are intended to exemplify non-limiting embodiments of the invention.

20

5. Definitions

The phrase "pharmaceutically acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic groups that may be present in the compounds of the invention. Compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable salts of such basic compounds are those that form salts comprising pharmacologically acceptable anions including, but not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, bromide, iodide, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydroxynaphthoate, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, muscate, napsylate, nitrate, panthenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, succinate, sulfate, tannate, tartrate, teoclate, triethylidide, and pamoate (*i.e.*, 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)). Compounds of the invention that include an amino moiety also can form

pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, 5 sodium, lithium, zinc, potassium, and iron salts.

As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

10 As used herein, the term "hydrate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "clathrate" means a compound of the invention or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a 15 solvent or water) trapped within.

As used herein, the term "alkyl group" means a saturated, monovalent, unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, (C₁-C₈)alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-20 propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, neopentyl, and hexyl, heptyl, and octyl. An alkyl group can be unsubstituted or substituted with one or two suitable substituents.

An "alkenyl group" means a monovalent, unbranched or branched hydrocarbon 25 chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to (C₂-C₈)alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butene, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one 30 or two suitable substituents.

An "alkynyl group" means monovalent, unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C₂-C₈)alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl,

hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted with one or two suitable substituents.

- An "aryl group" means a monocyclic or polycyclic-aromatic group comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzofused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted with one or more suitable substituents. Preferably, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryl".
- 10 A "heteroaryl group" means a monocyclic or polycyclic aromatic ring comprising carbon atoms and one or more heteroatoms, preferably, 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Preferred heteroaryl-ring systems include 5 to 6 membered monocyclic, 8 to 11 membered bicyclic, and 11 to 15 membered tricyclic ring systems. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, phenyl, isoxazolyl, and 15 oxazolyl. A heteroaryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, a heteroaryl group is a 5 or 6 membered monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as "(C₂-C₅)heteroaryl", which optionally can be fused to one or more other aryl, cycloalkyl, heteroaryl, or heterocyclic ring systems to form 7 to 10 membered bicyclic or 10 to 15 membered tricyclic ring systems.

A "cycloalkyl group" means a non-aromatic, monocyclic or polycyclic ring comprising carbon and hydrogen atoms. A cycloalkyl group can have one or more carbon-carbon double bonds in the ring so long as the ring is not rendered aromatic by their presence. Examples of cycloalkyl groups include, but are not limited to, (C₃-C₈)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes and (C₃-C₈)cycloalkenyl groups, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl, and unsaturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl group is a 30 monocyclic ring or bicyclic ring.

A “heterocycloalkyl group” means a non-aromatic monocyclic or polycyclic ring comprising carbon atoms and at least one heteroatom, preferably, 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Preferred heterocyclic-ring systems include 3 to 8 membered monocyclic, 8 to 11 membered bicyclic, and 11 to 15 membered tricyclic ring systems. A heterocycloalkyl group can have one or more carbon-carbon double bonds or carbon-heteroatom double bonds in the ring as long as the ring is not rendered aromatic by their presence. Examples of heterocycloalkyl groups include aziridinyl, pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a 3-7 membered monocyclic ring, wherein the ring comprises from 1 to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as “(C₁-C₆)heterocycloalkyl”, which optionally can be fused to one or more other aryl, cycloalkyl, heteroaryl, or heterocyclic ring systems to form 7 to 10 membered bicyclic or 10 to 15 membered tricyclic ring systems.

The term “alkoxy group” means an -O-alkyl group, wherein alkyl is as defined above. An alkoxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the alkyl chain of an alkoxy group is from 1 to 8 carbon atoms in length, referred to herein as “(C₁-C₈)alkoxy”.

The term “aryloxy group” means an O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as “(C₆)aryloxy”.

25 The term “benzyl” means CH₂-phenyl. A benzyl group can be unsubstituted or substituted with one or more suitable substituents.

The term “phenyl” means C₆H₅. A phenyl group can be unsubstituted or substituted with one or more suitable substituents.

A “carbonyl” group is a divalent group of the formula -C(O)-.

30 An “alkoxycarbonyl” group means a monovalent group of the formula C(O)-alkoxy. Preferably, the hydrocarbon chain of an alkoxycarbonyl group is from 1 to 8 carbon atoms in length, referred to herein as a “lower alkoxycarbonyl” group.

As used herein, “halogen” means fluorine, chlorine, bromine, or iodine. Correspondingly, the meaning of the term “halo” encompass fluoro, chloro, bromo, and iodo.

As used herein, a "suitable substituent" means a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: (C₁–C₈)alkyl; (C₁–C₈)alkenyl; (C₁–C₈)alkynyl; aryl; (C₂–C₅)heteroaryl;

5 (C₁–C₆)heterocycloalkyl; (C₃–C₇)cycloalkyl; O–(C₁–C₈)alkyl; O–(C₁–C₈)alkenyl; O–(C₁–C₈)alkynyl; O–aryl; CN; OH; oxo; halo, C(O)OH; COhalo; O(CO)halo; CF₃, N₃; NO₂, NH₂; NH((C₁–C₈)alkyl); N((C₁–C₈)alkyl)₂; NH(aryl); N(aryl)₂; (CO)NH₂; (CO)NH((C₁–C₈)alkyl); (CO)N((C₁–C₈)alkyl)₂; (CO)NH(aryl); (CO)N(aryl)₂; O(CO)NH₂; NHOH; NOH((C₁–C₈)alkyl); NOH(aryl); O(CO)NH((C₁–C₈)alkyl); O(CO)N((C₁–C₈)alkyl)₂;

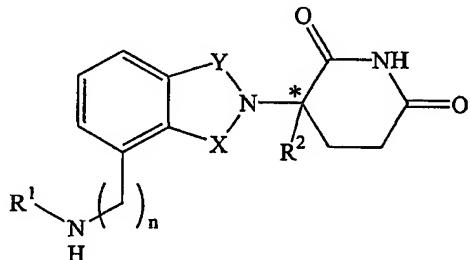
10 O(CO)NH(aryl); O(CO)N(aryl)₂; CHO; CO((C₁–C₈)alkyl); CO(aryl); C(O)O((C₁–C₈)alkyl); C(O)O(aryl); O(CO)((C₁–C₈)alkyl); O(CO)(aryl); O(CO)O((C₁–C₈)alkyl); O(CO)O(aryl); S–(C₁–C₈)alkyl; S–(C₁–C₈)alkenyl; S–(C₁–C₈)alkynyl; and S–aryl. One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

15

6. Detailed Description of The Invention

In one embodiment, the invention encompasses compounds of the formula:

20



25 or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH₂ or C=O;

30 R¹ is H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, C(O)R³, C(S)R³, C(O)OR⁴, (C₁–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, C(O)NHR³, C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁–C₈)alkyl–O(CO)R⁵;

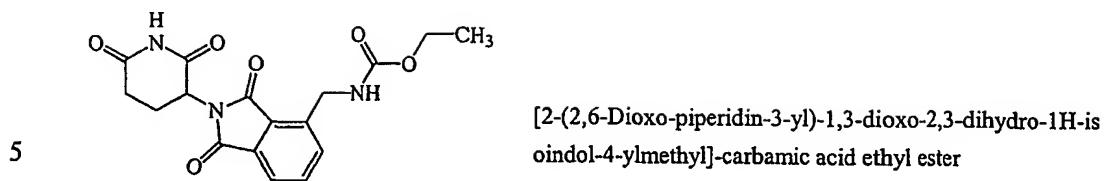
35 R² is H, F, benzyl, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, or (C₂–C₈)alkynyl;

- R^3 and R^3' are independently (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_0-C_8) alkyl-N(R^6)₂, (C_1-C_8) alkyl-OR⁵,
- 5 (C_1-C_8) alkyl-C(O)OR⁵, (C_1-C_8) alkyl-O(CO)R⁵, or C(O)OR⁵;
- R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl-OR⁵, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, or (C_0-C_4) alkyl- (C_2-C_5) heteroaryl;
- 10 R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl; each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl-C(O)O-R⁵ or the R^6 groups can join to form a heterocycloalkyl group;
- 15 n is 0 or 1; and
the * represents a chiral-carbon center;
with the proviso that when n is 0 then R¹ is not H.
- In a separate embodiment of compounds of formula I, when n is 0 then R¹ is (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl,
- 20 (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, C(O)R³, C(O)OR⁴, (C_1-C_8) alkyl-N(R^6)₂, (C_1-C_8) alkyl-OR⁵, (C_1-C_8) alkyl-C(O)OR⁵, or (C_1-C_8) alkyl-O(CO)R⁵;
- R^2 is H or (C_1-C_8) alkyl; and
- 25 R^3 is (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_5-C_8) alkyl-N(R^6)₂; (C_0-C_8) alkyl-NH-C(O)O-R⁵; (C_1-C_8) alkyl-OR⁵, (C_1-C_8) alkyl-C(O)OR⁵, (C_1-C_8) alkyl-O(CO)R⁵, or C(O)OR⁵; and the other variables have
- 30 the same definitions. Further, the compounds encompassed by Formulas II, III, IV, V, VI, and VII as described above are also included within the invention.

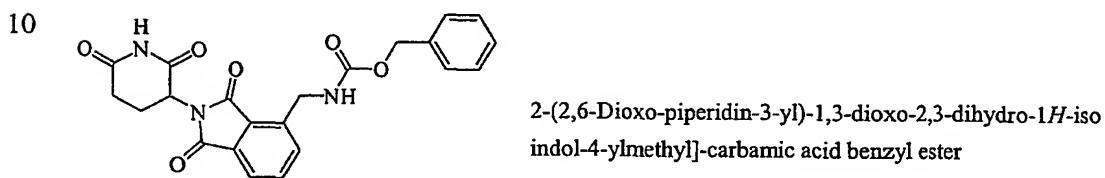
A few examples of compounds of the invention which are illustrative and non-limiting are depicted in Table 1 below.

TABLE 1: Examples of Compounds of the Invention

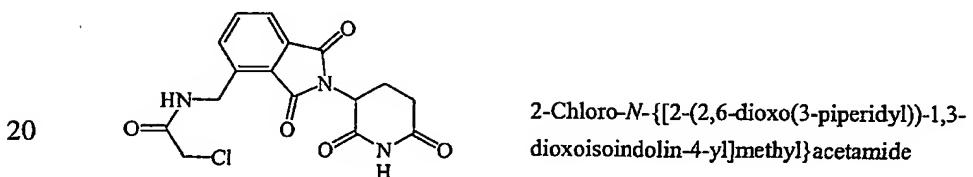
	Structure	Name
5		[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1 <i>H</i> -isooindol-4-yl-methyl]-carbamic acid <i>tert</i> -butyl ester
10	I-1	
15		4-(Aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione
20	I-2	
25		<i>N</i> -[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1 <i>H</i> -isooindol-4-yl-methyl]-acetamide
30	I-3	
35		<i>N</i> -{[2-(2,6-Dioxo(3-piperidyl)-1,3-dioxoisooindolin-4-yl]methyl}cyclopropyl-carboxamide
	I-4	



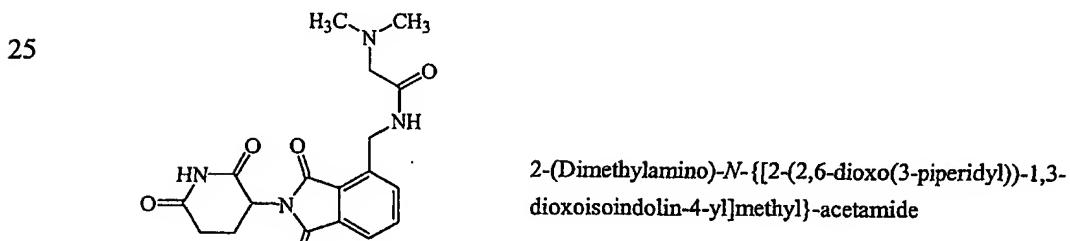
I-5



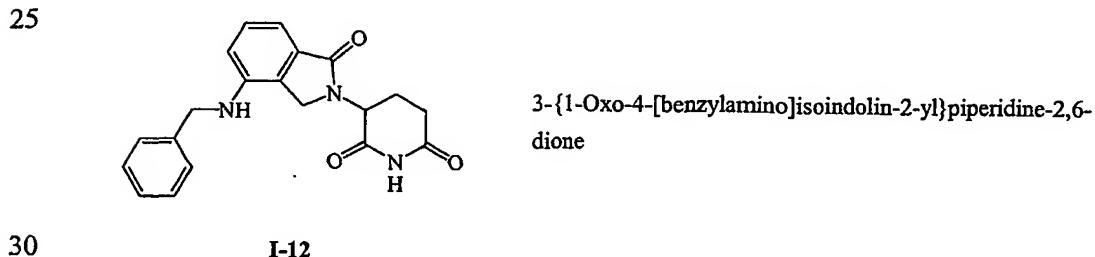
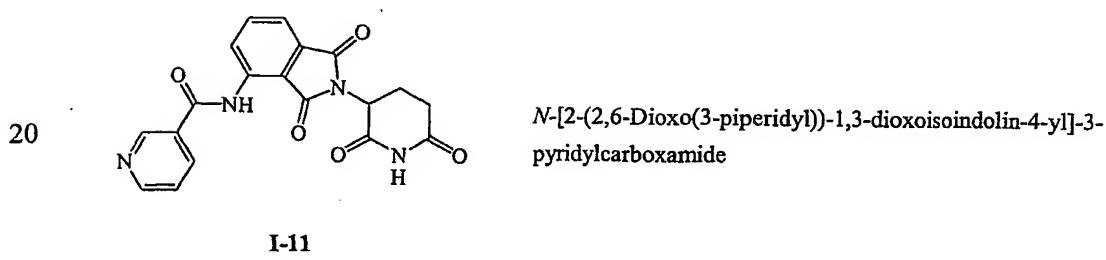
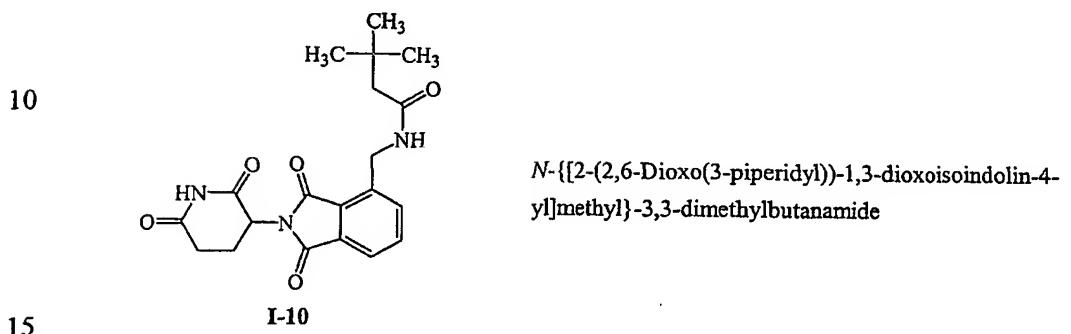
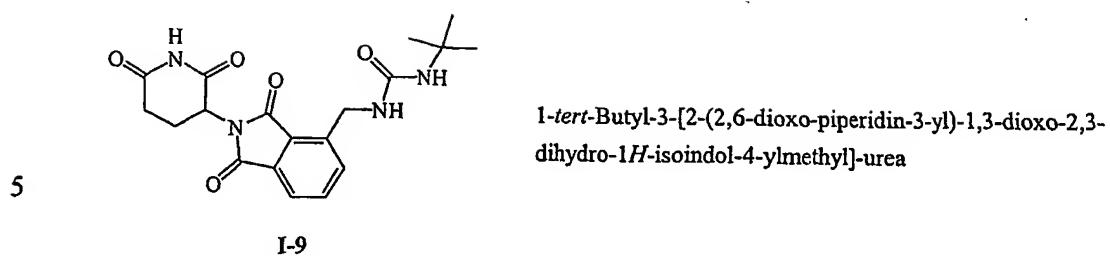
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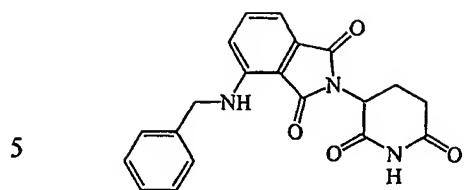


I-7



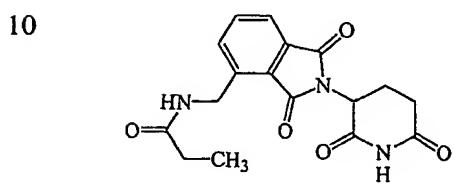
I-8





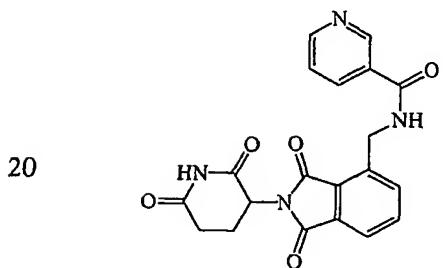
2-(2,6-Dioxo(3-piperidyl))-4-[benzylamino]isoindoline-1,3-dione

I-13



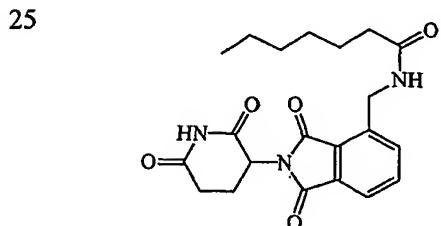
N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}propanamide

15 I-14



N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}-3-pyridylcarboxamide

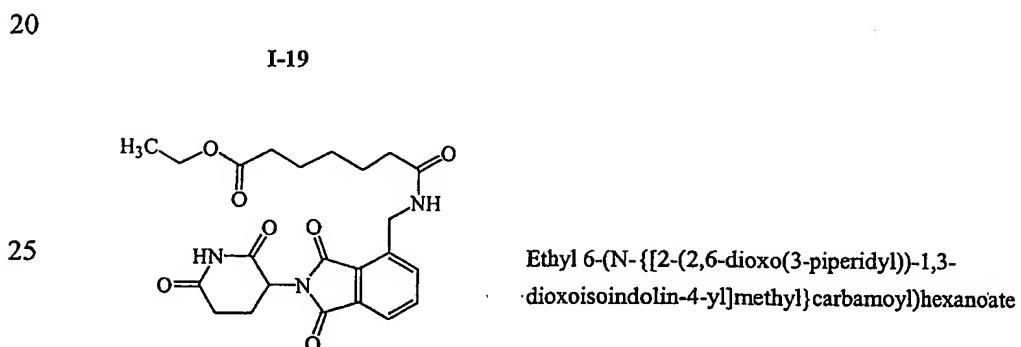
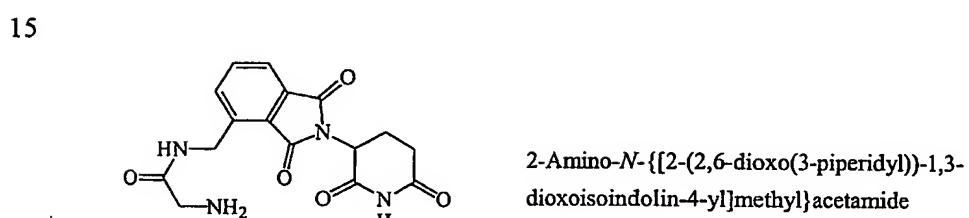
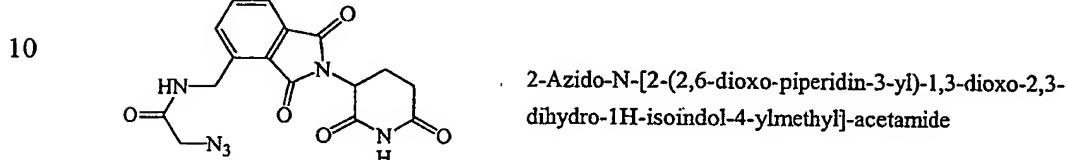
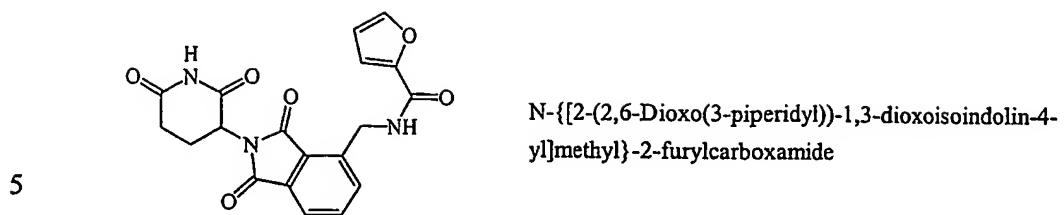
I-15



N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}heptanamide

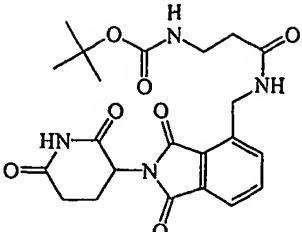
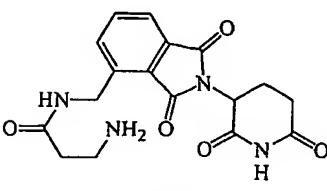
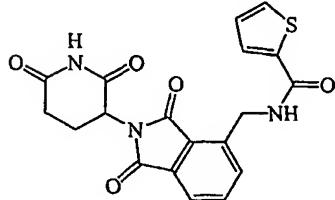
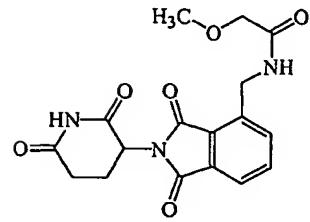
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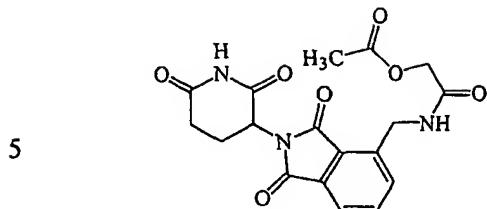
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- 5 
I-21
- 10 
I-22
- 15 
I-23
- 20 
I-24

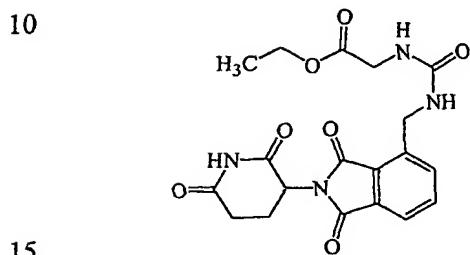
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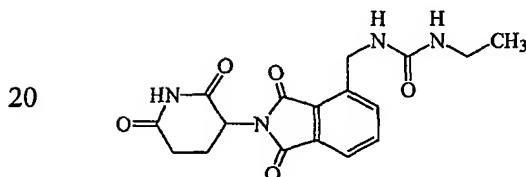
(*N*-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}carbamoyl)methyl acetate

I-25



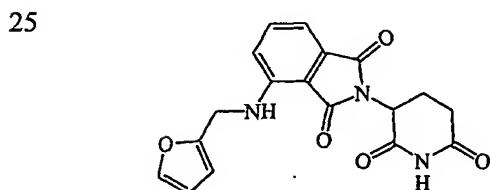
Ethyl 2-[(*N*-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}carbamoyl)amino]acetate

I-26



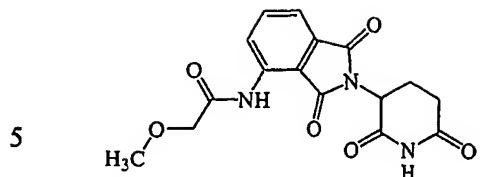
N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(ethylamino)carboxamide

I-27



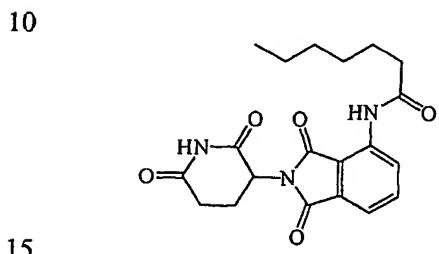
2-(2,6-Dioxo(3-piperidyl))-4-[(2-furylmethyl)amino]isoindoline-1,3-dione

35



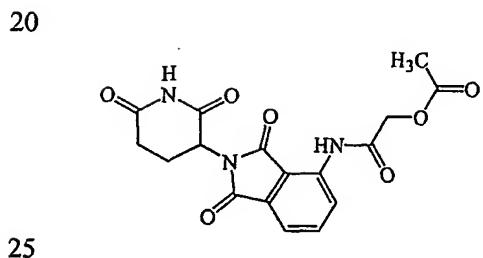
N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-methoxyacetamide

I-29



N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]heptanamide

I-30

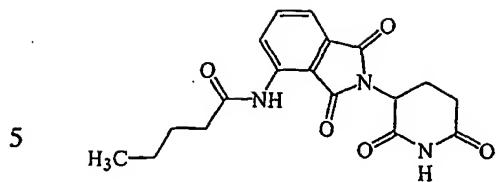


{*N*-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]carbamoyl}methyl acetate

I-31

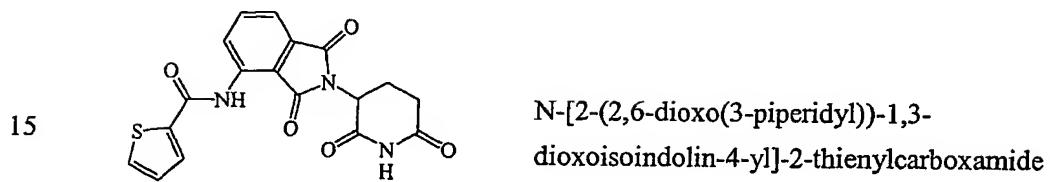
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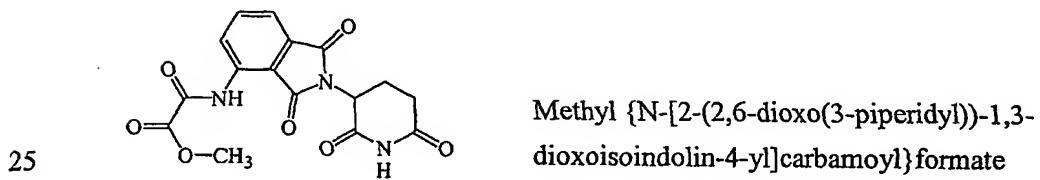
I-32

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I-33

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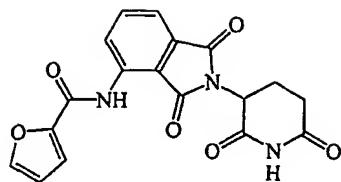


I-34

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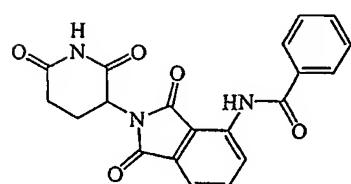
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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-furylcarboxamide

I-35

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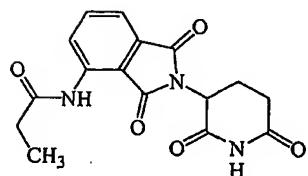


N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]benzamide

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I-36

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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]propanamide

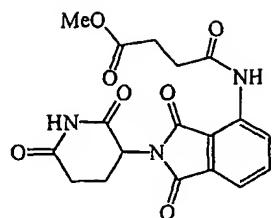
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I-37

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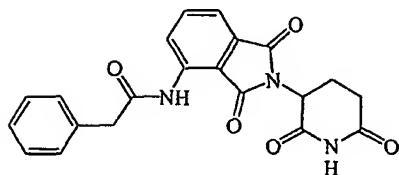
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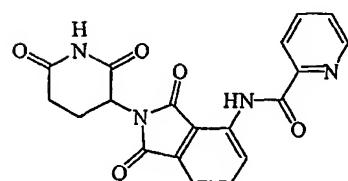
**I-38**

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**I-39**

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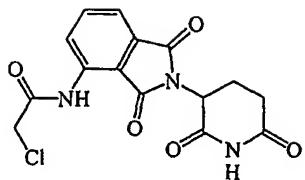
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I-40

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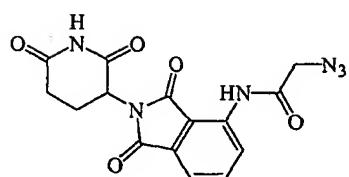
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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]-2-chloroacetamide

I-41

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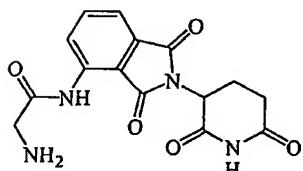


2-azido-*N*-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]acetamide

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I-42

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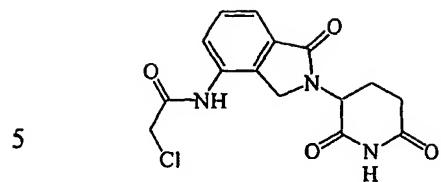
2-Amino-*N*-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]acetamide

25

I-43

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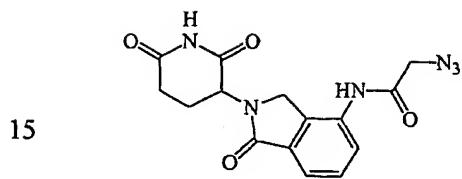
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N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]-2-chloroacetamide

I-44

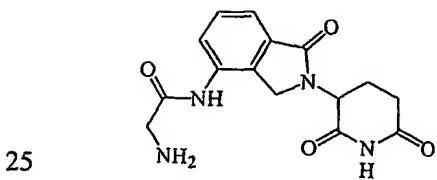
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2-azido-*N*-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]acetamide

I-45

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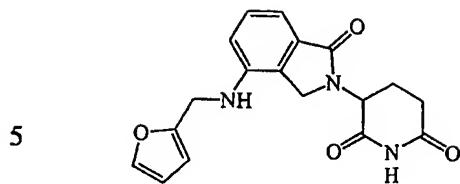


2-Amino-*N*-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]acetamide

I-46

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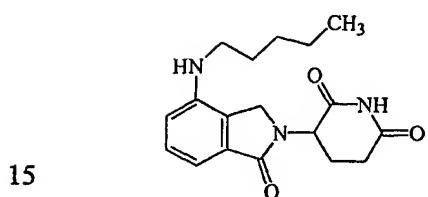
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3-{4-[(2-Furylmethyl)amino]-1-oxoisoindolin-2-yl}piperidine-2,6-dione

I-47

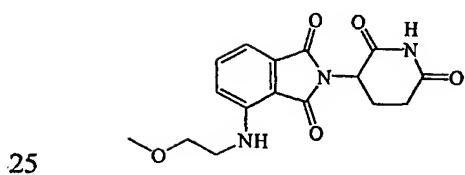
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3-[1-Oxo-4-(pentylamino)isoindolin-2-yl]piperidine-2,6-dione

I-48

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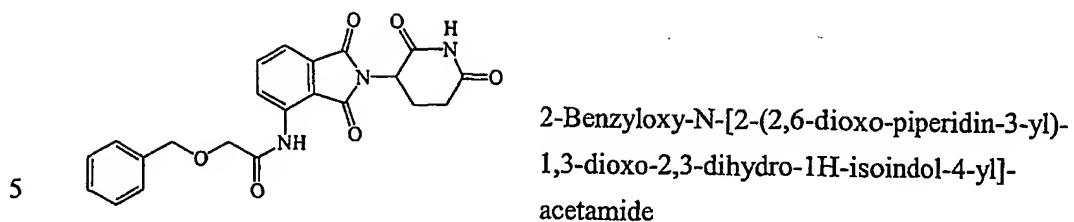


2-(2,6-Dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione

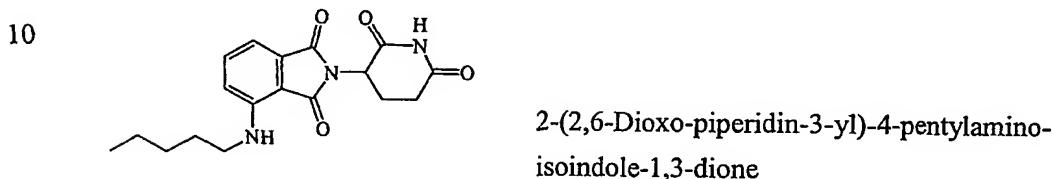
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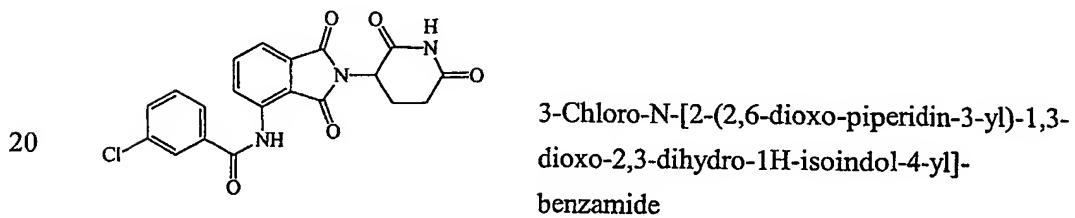
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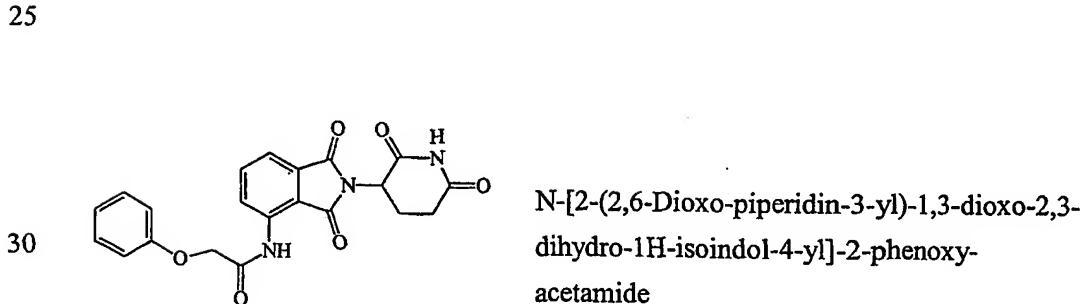
I-50



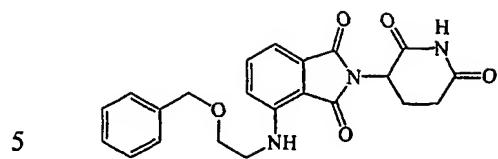
I-51



I-52

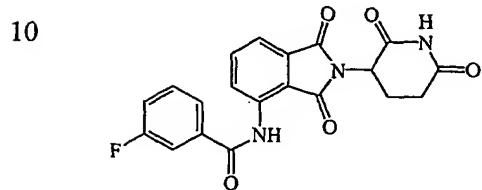


I-53



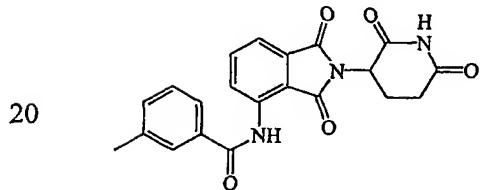
4-(2-Benzylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione

I-54



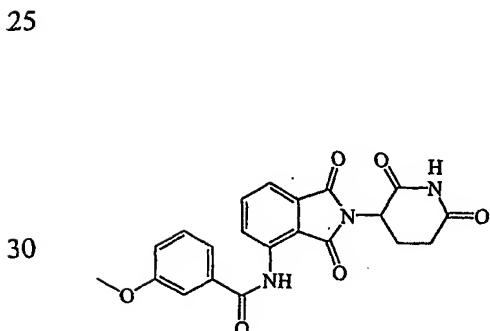
N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-benzamide

15
I-55



N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methyl-benzamide

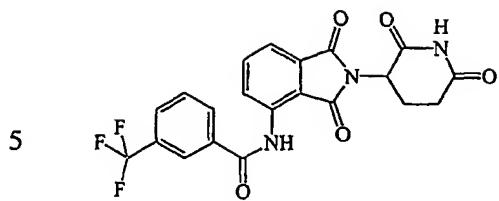
I-56



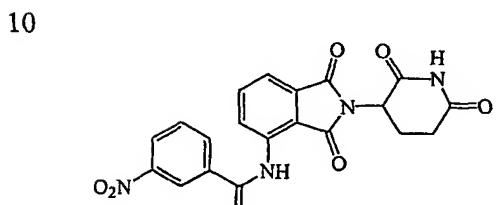
N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-benzamide

I-57

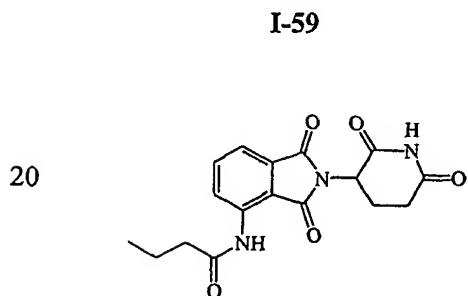
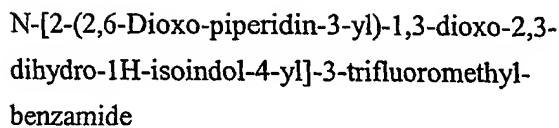
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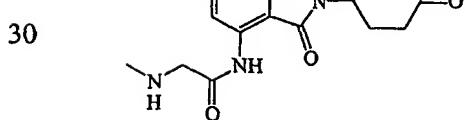
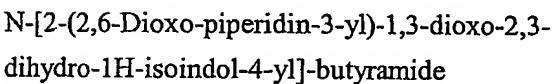
I-58



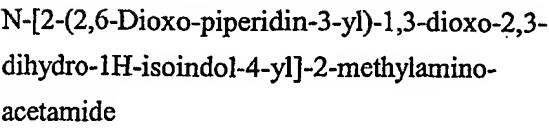
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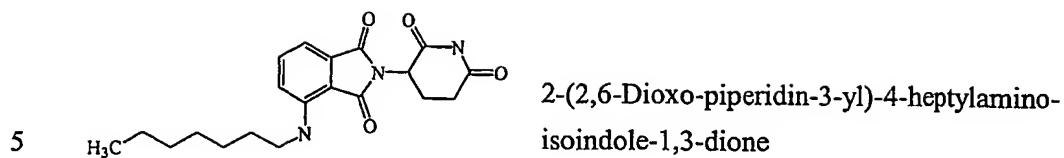


I-59

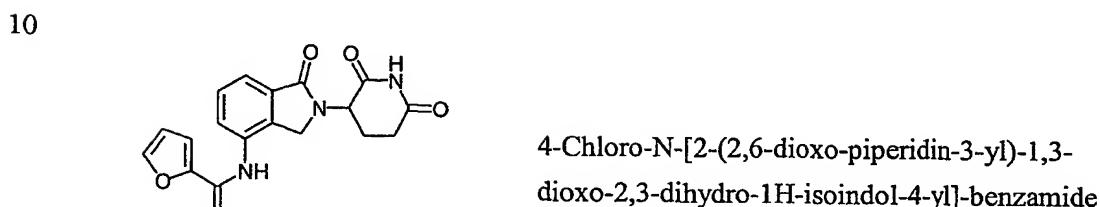


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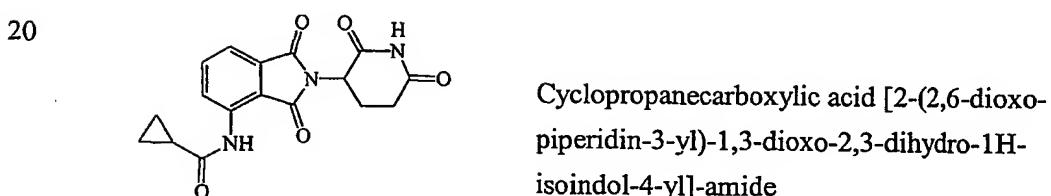


I-62



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I-63



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I-64

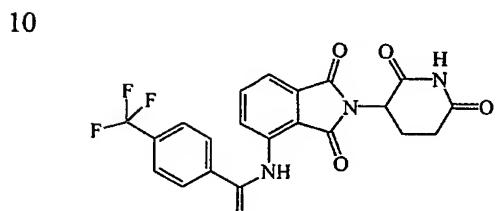
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-fluoro-benzamide

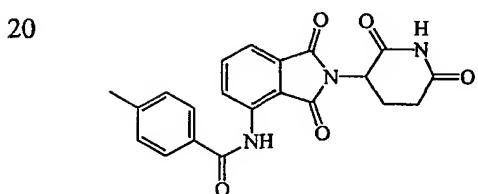
I-65



N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-trifluoromethyl-benzamide

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I-66



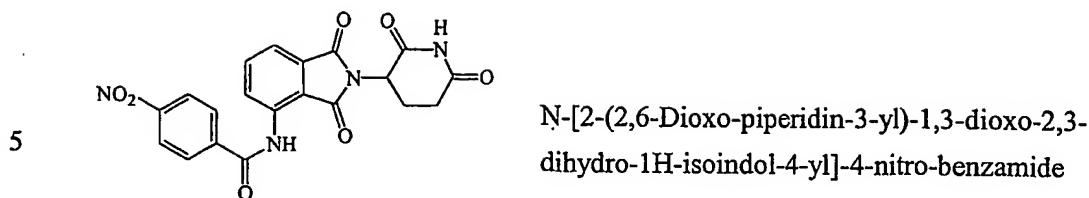
N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methyl-benzamide

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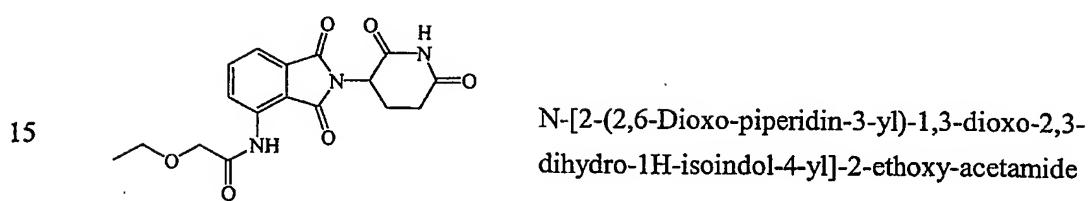
I-67

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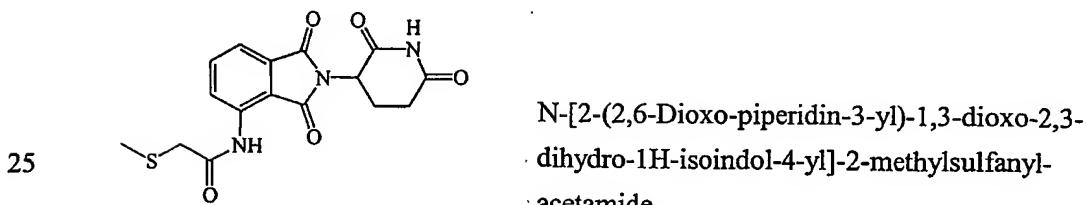
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**I-68**

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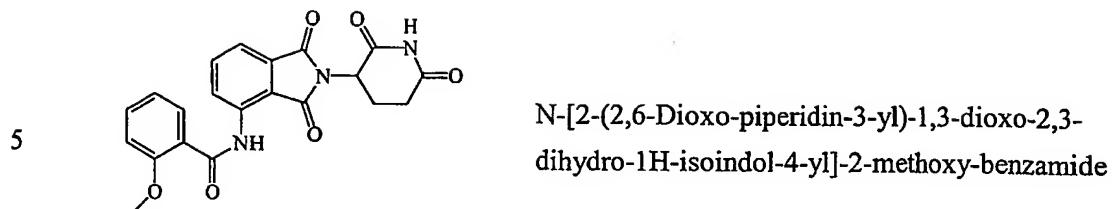
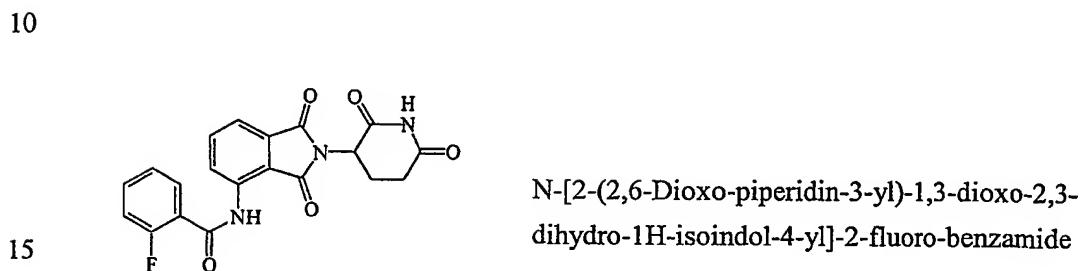
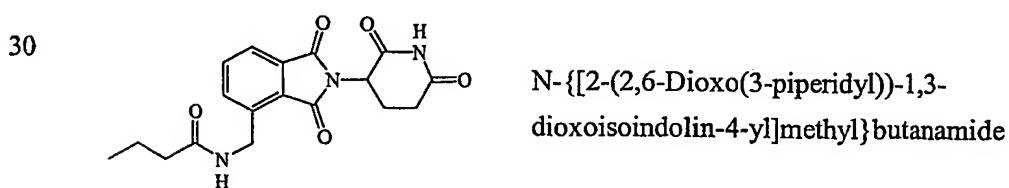
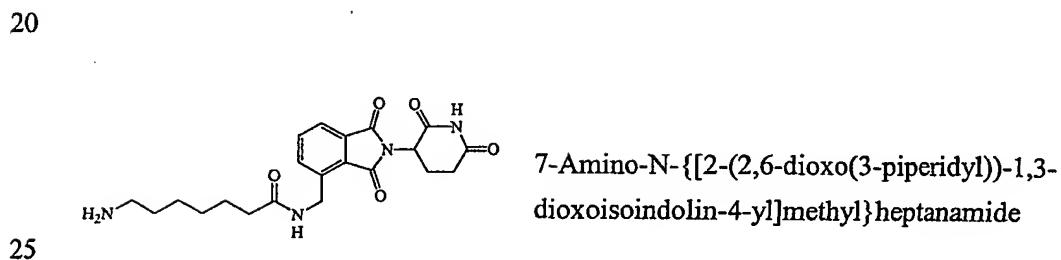
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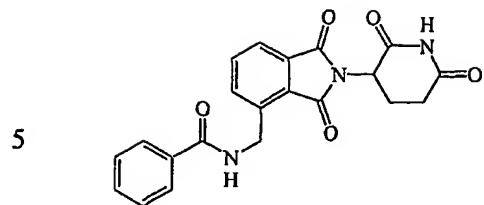
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**I-71****I-72**

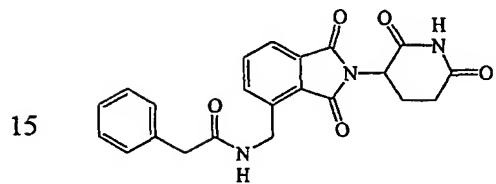
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}benzamide

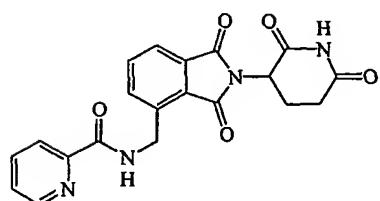
I-75

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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}phenylacetamide

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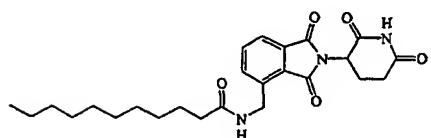


N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}-2-pyridylcarboxamide

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I-77

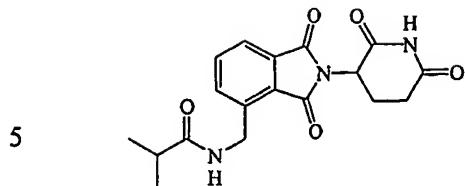
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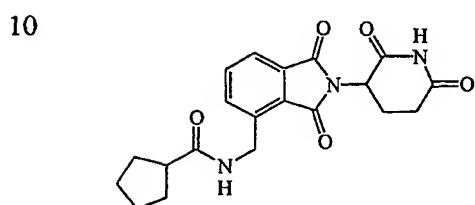
N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}undecamide

35

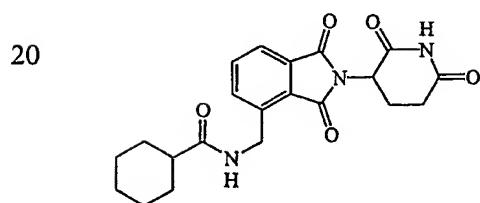
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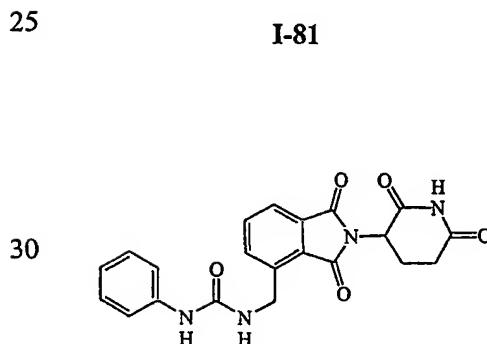
N-*{*[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl*}*-2-methylpropanamide



N-*{*[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl*}*cyclopentylcarboxamide



N-*{*[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl*}*cyclohexylcarboxamide

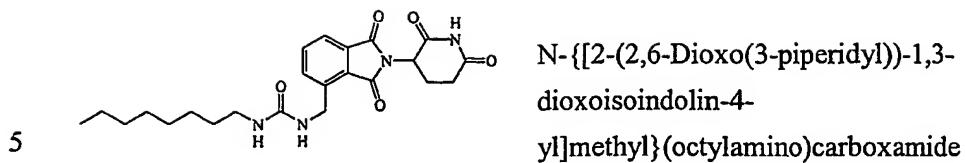
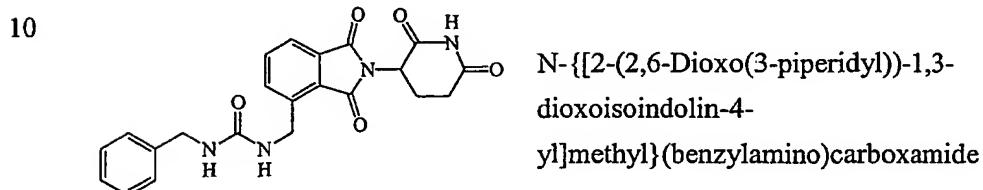
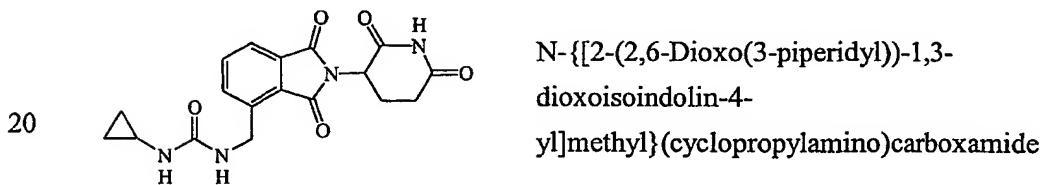
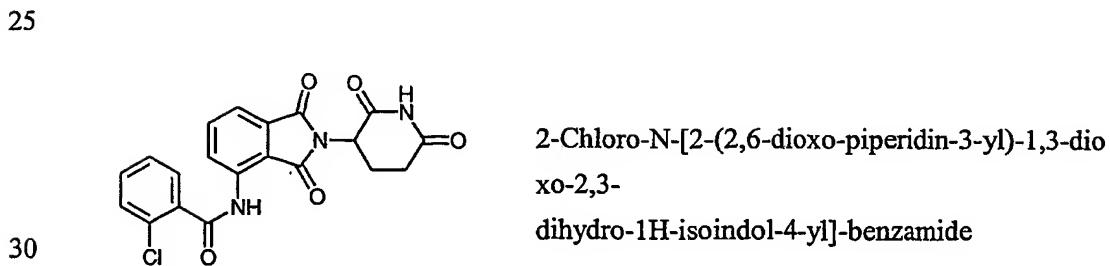


N-*{*[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl*}*(phenylamino)carboxamide

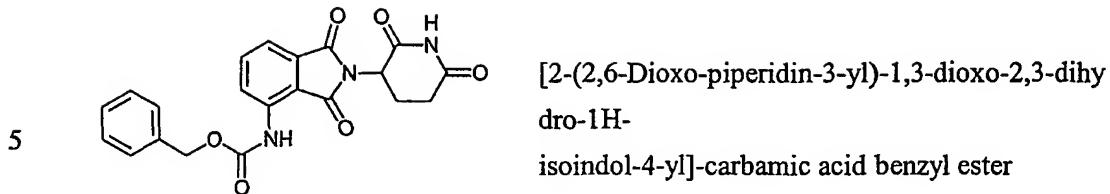


TABLE 1 Cont.

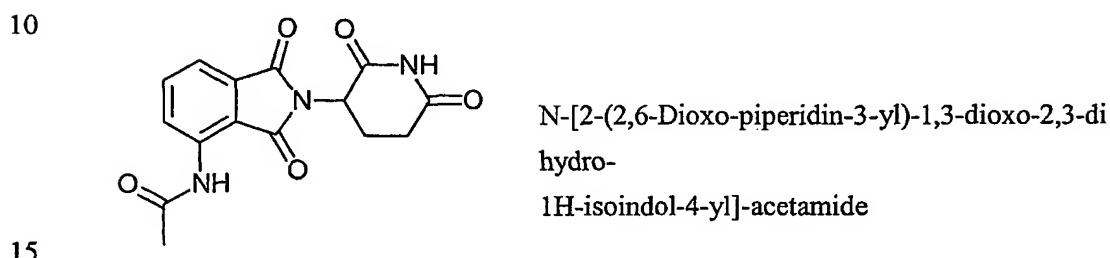
	Structure	Name
5		N-[(2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl](butylamino)carboxamide
10	I-83	
15		N-[(2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl](propylamino)carboxamide
20	I-84	
25		N-[(2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl](cyclohexylamino)carboxamide
30	I-85	
35		N-[(2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl][(methylethylamino)]carboxamide
	I-86	

**I-87****I-88****I-89****I-90**

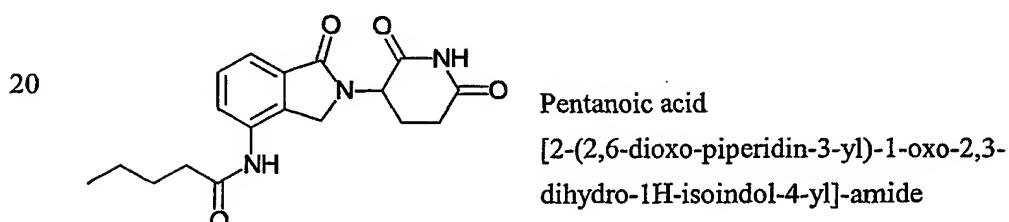
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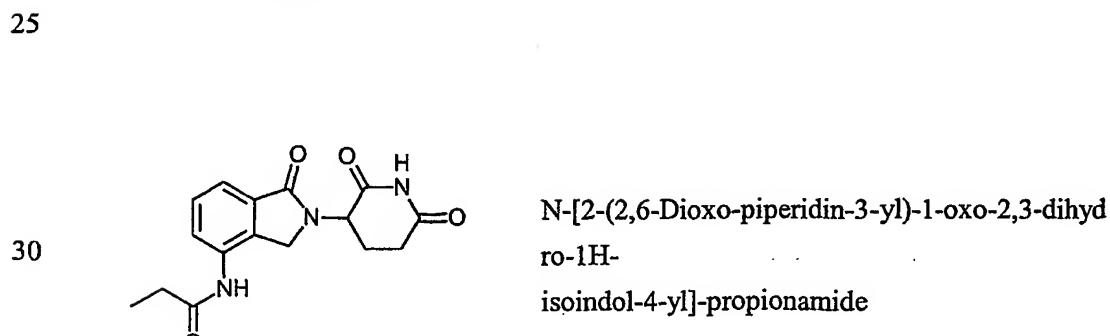
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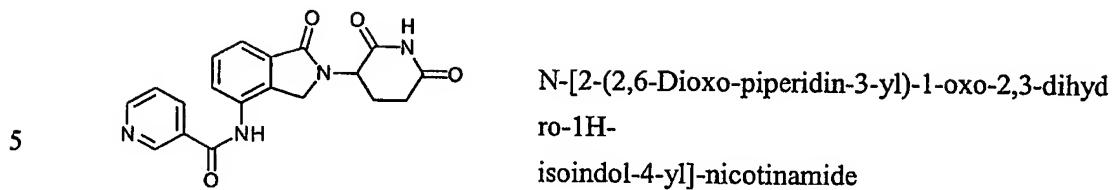
I-92



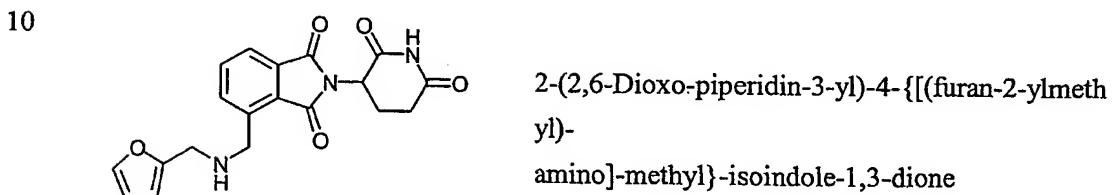
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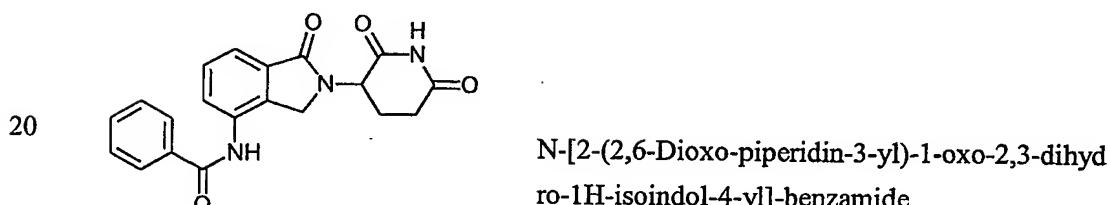
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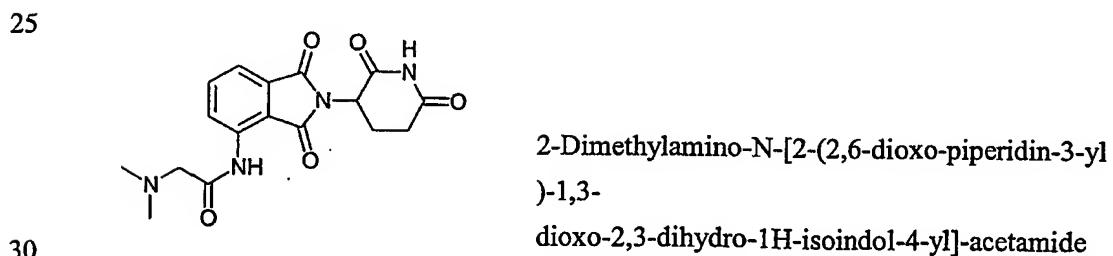
I-95



I-96

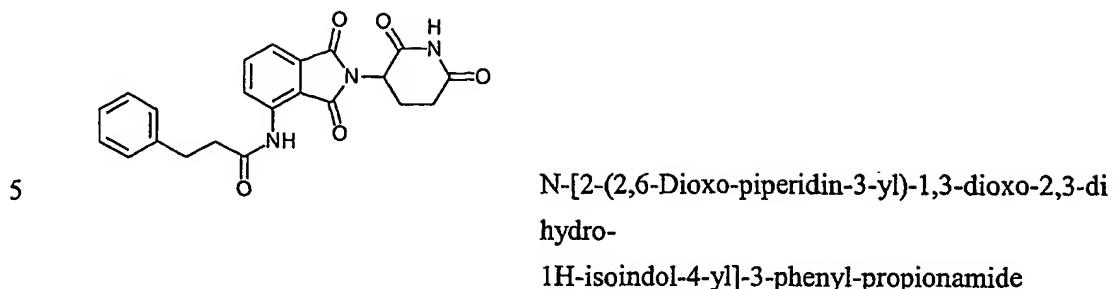


I-97



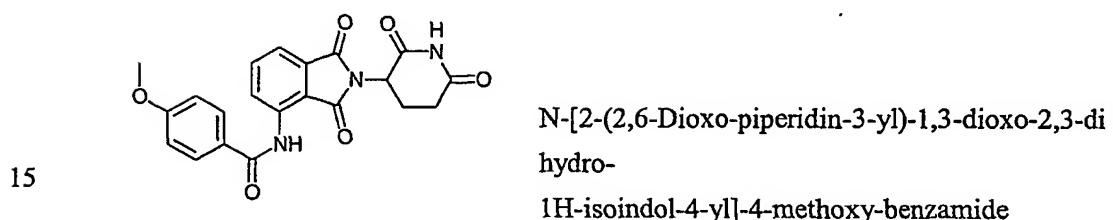
I-98

5		N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methyl-benzamide
10		Heptanoic acid [2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-amide
15		N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3,3-dimethylbutyramide
20		N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-isobutyramide
25		I-101
30		I-102
35		



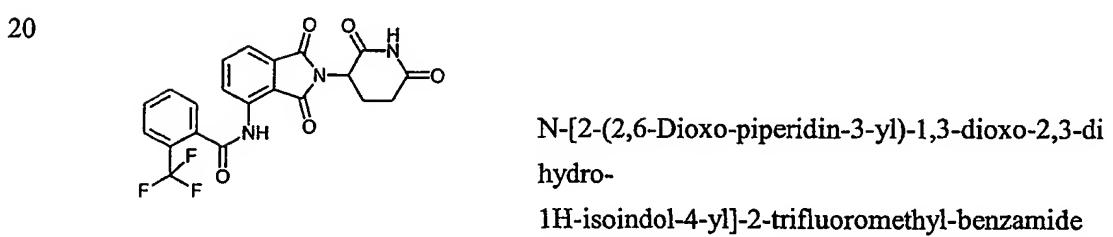
I-103

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I-104

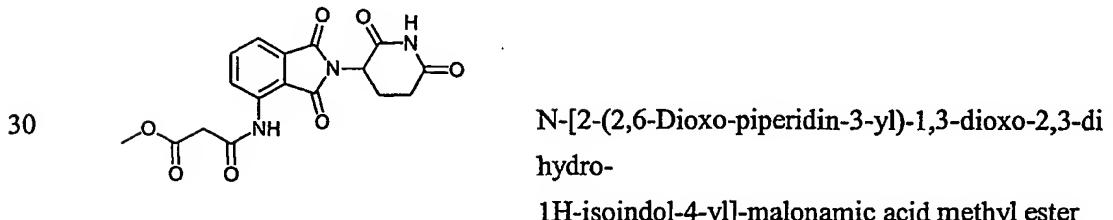
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I-105

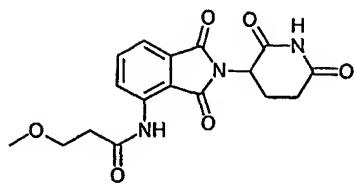
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L-106

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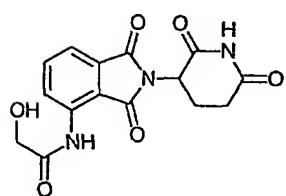
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-
1H-isoindol-4-yl]-3-methoxy-propionamide

I-107

10

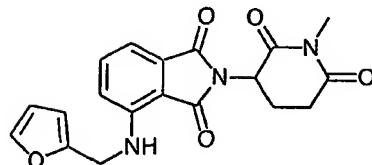


N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-
1H-isoindol-4-yl]-2-hydroxy-acetamide

15

I-108

20

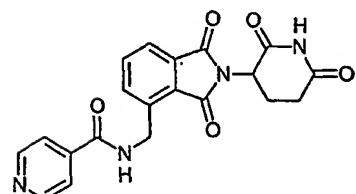


4-[(Furan-2-ylmethyl)-amino]-2-(1-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione

25

I-109

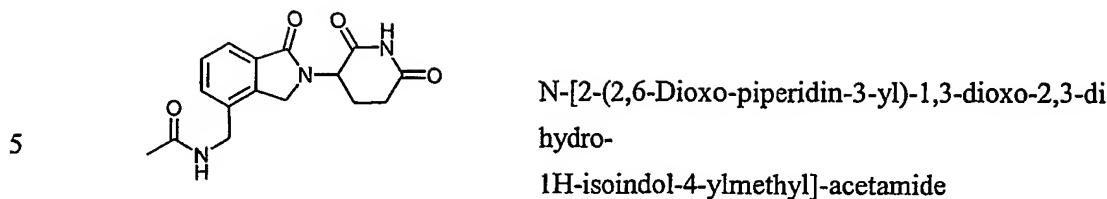
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-
1H-isoindol-4-ylmethyl]-isonicotinamide

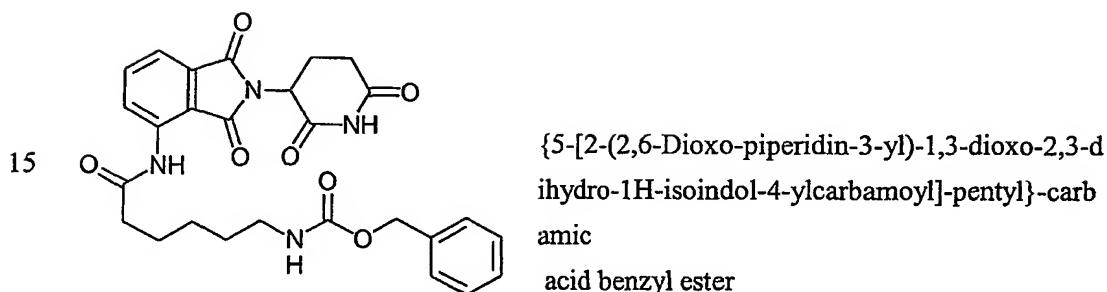
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I-110



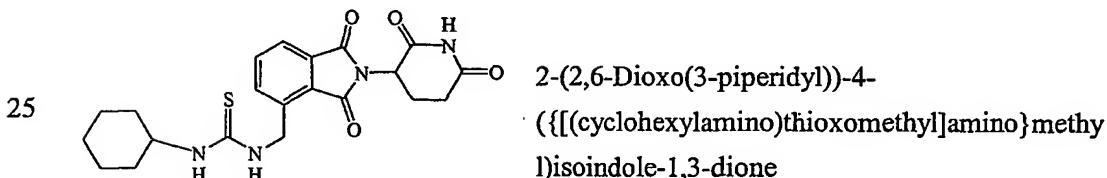
I-111

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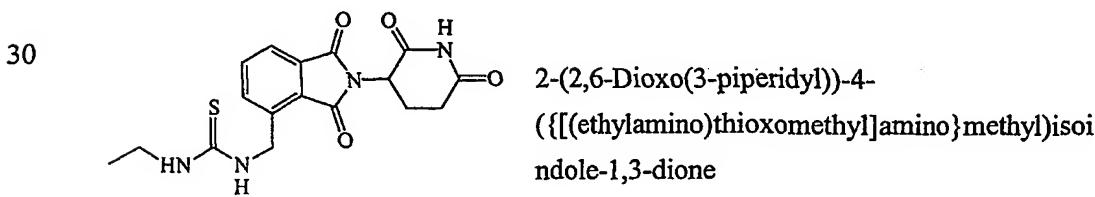


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I-112

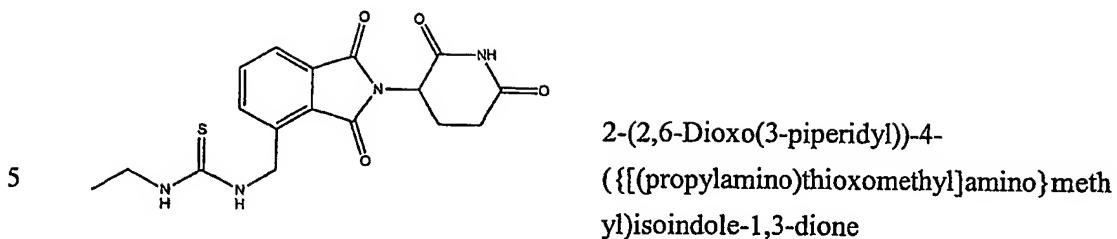


L-113

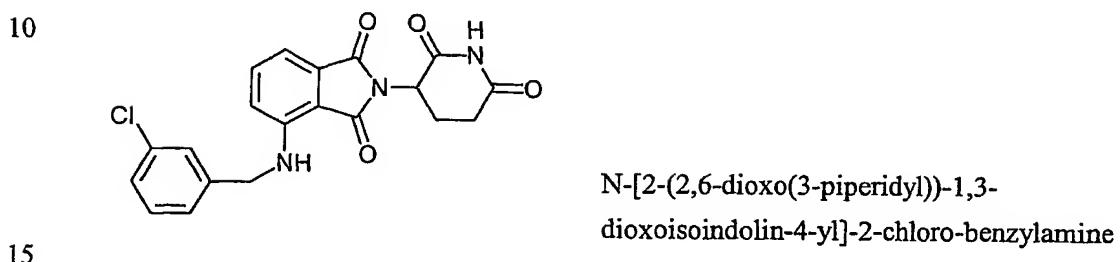


I-114

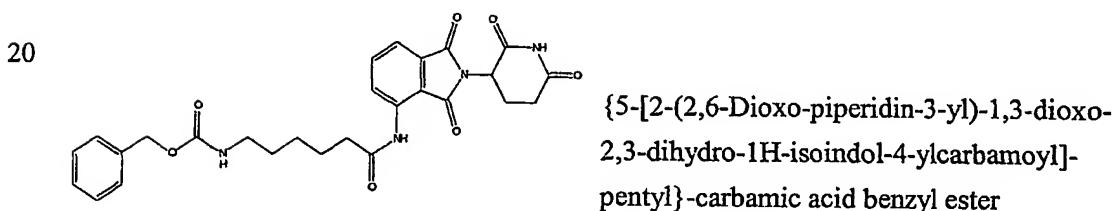
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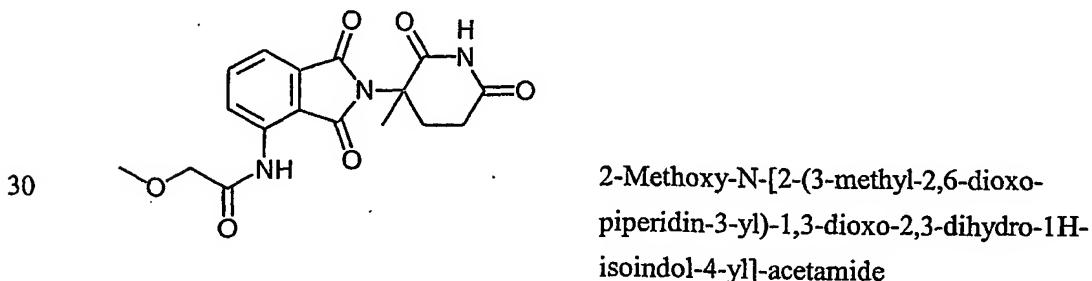
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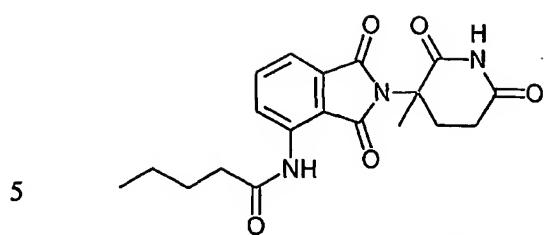
I-116



25 I-117

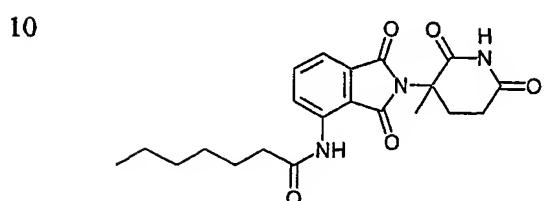


J-118



Pentanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide

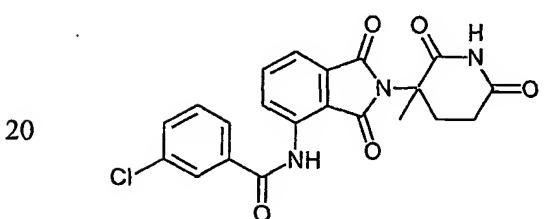
L-119



Heptanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-amide

15

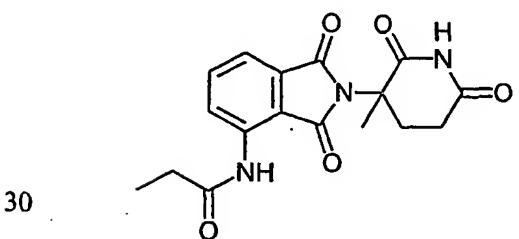
I-120



3-Chloro-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide

25

I-121

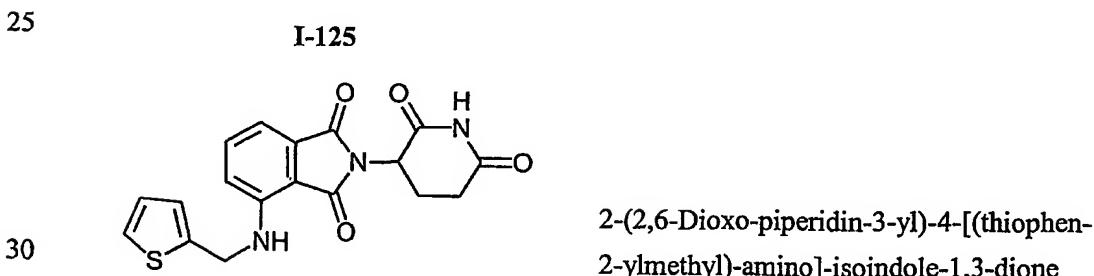
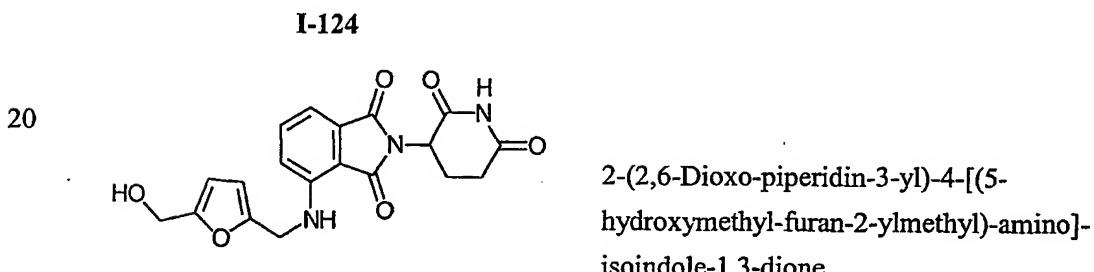
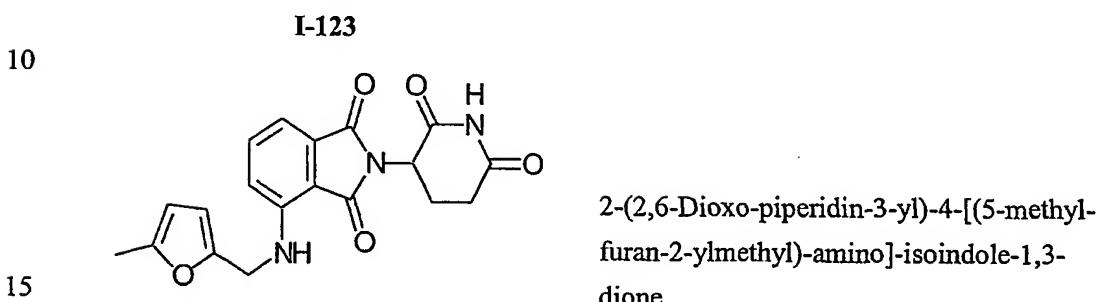
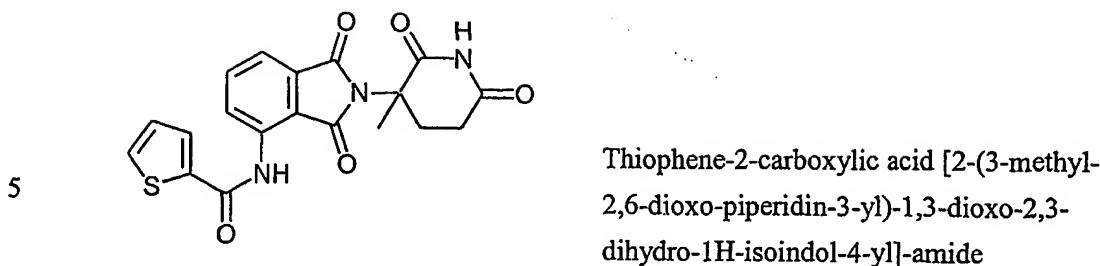


N-[2-(3-Methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-propionamide

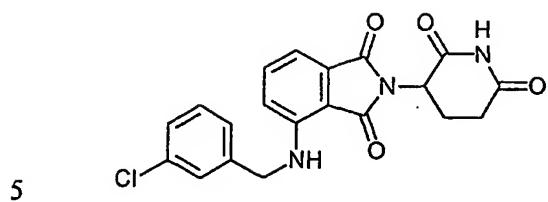
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I-122

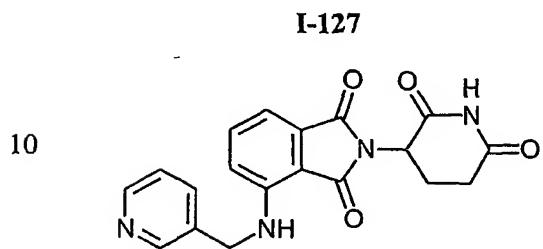
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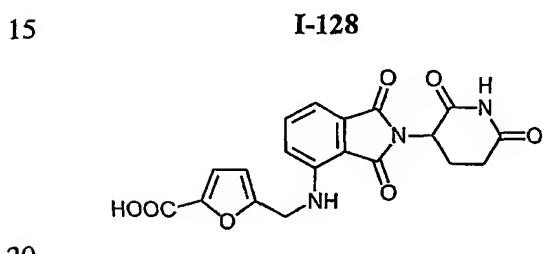
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I-126



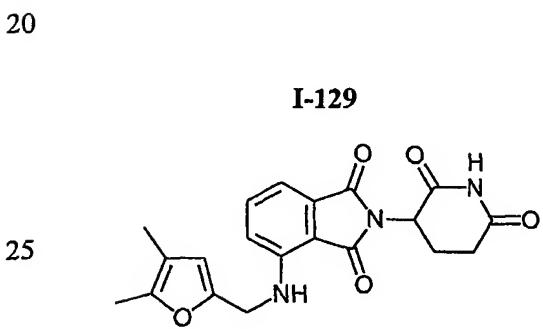
4-(3-Chloro-benzylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



2-(2,6-Dioxo-piperidin-3-yl)-4-[(pyridin-3-ylmethyl)-amino]-isoindole-1,3-dione



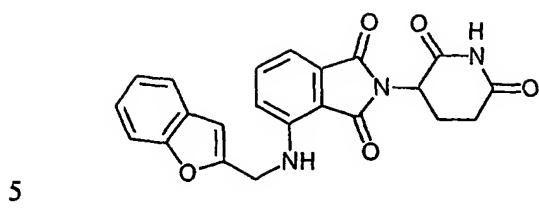
5-{[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylamino]-methyl}-furan-2-carboxylic acid



4-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione

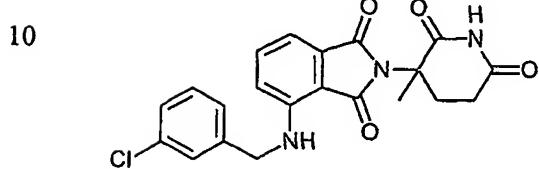


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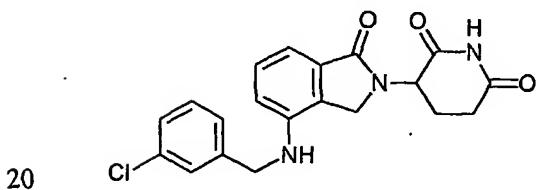
4-[(Benzofuran-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione

I-131



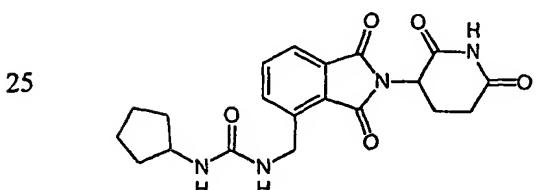
4-(3-Chloro-benzylamino)-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione

I-132



3-[4-(3-Chloro-benzylamino)-1-oxo-1,3-dihydro-isindol-2-yl]-piperidine-2,6-dione

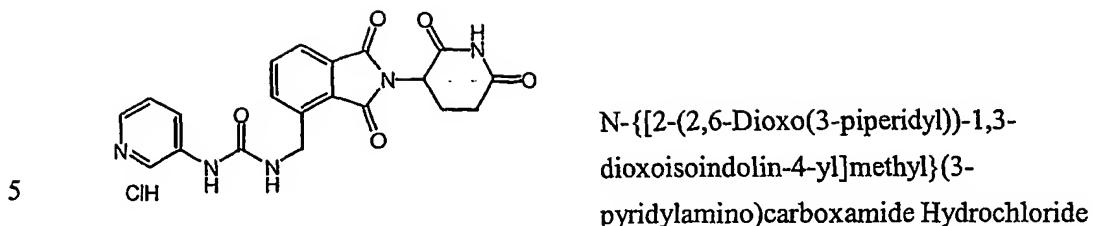
I-133



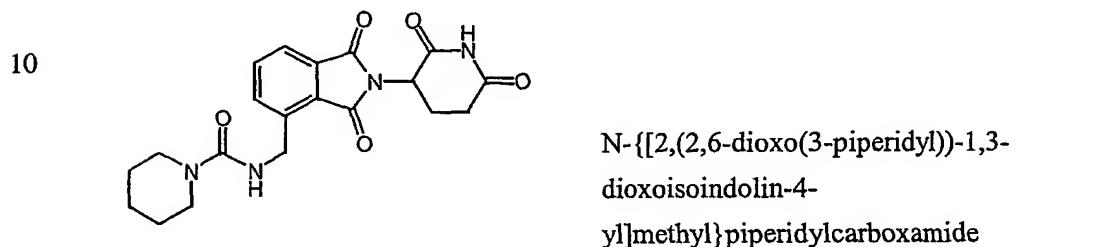
N-[[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl](cyclopentylamino)carboxamide

I-134

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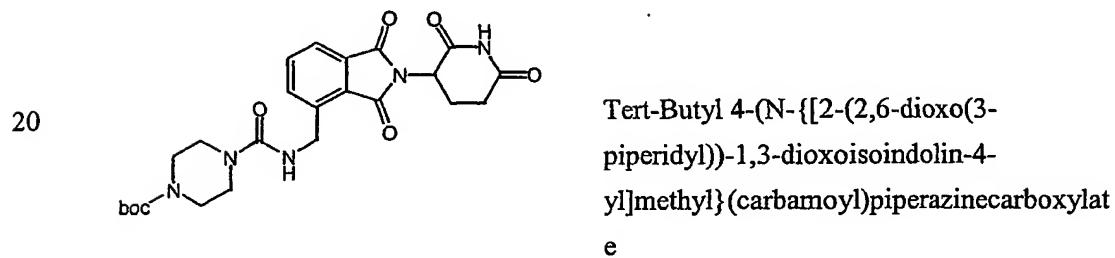


I-135



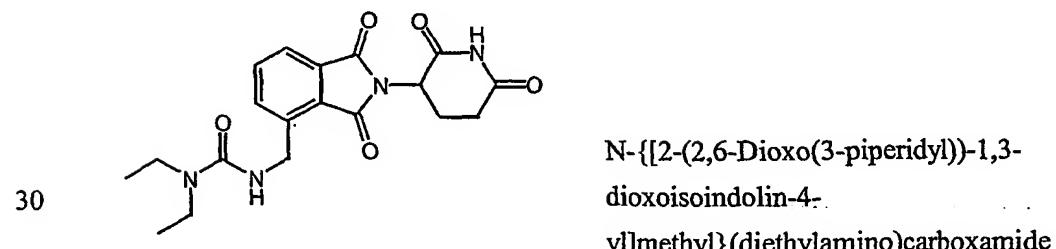
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I-136

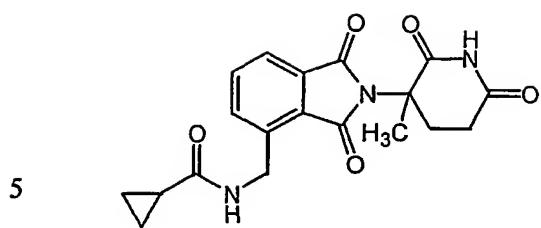


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I-137



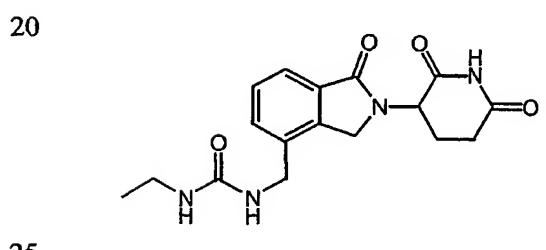
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Cyclopropyl-N-{{[2-(3-methyl-2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}carboxamide}

I-139

N-{{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisoindolin-4-yl]methyl}cyclopropylcarboxamide}

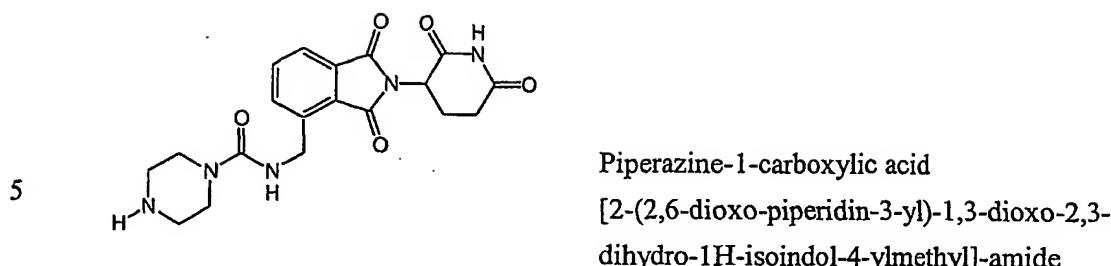
I-140

N-{{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisoindolin-4-yl]methyl}(ethylamino)carboxamide

I-141

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**I-142**

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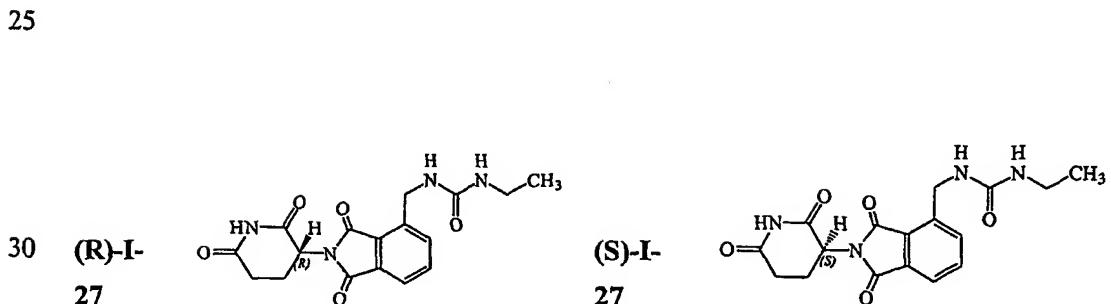
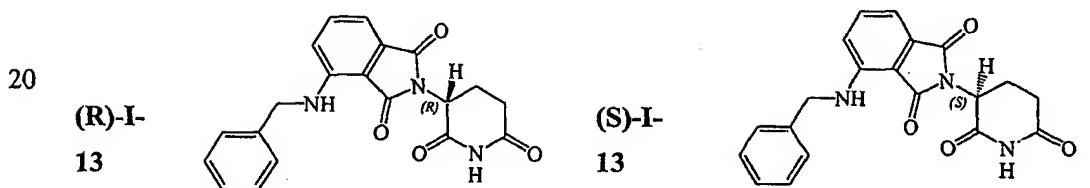
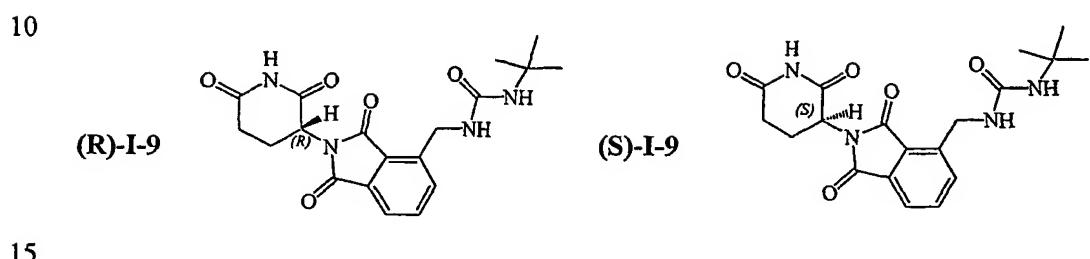
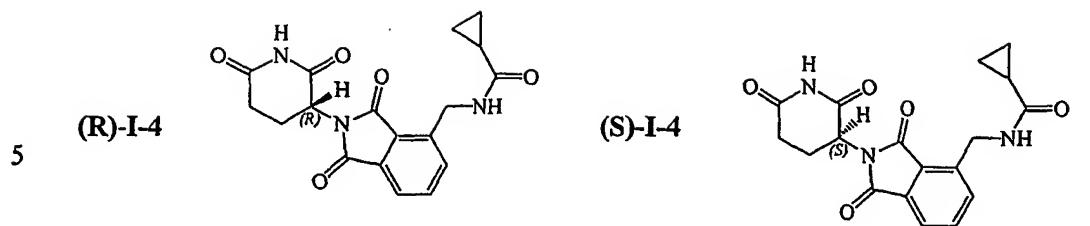
Selected compounds of Table 1 were tested using the *in vitro* assays described below and found to be active for modulating the production of TNF- α .

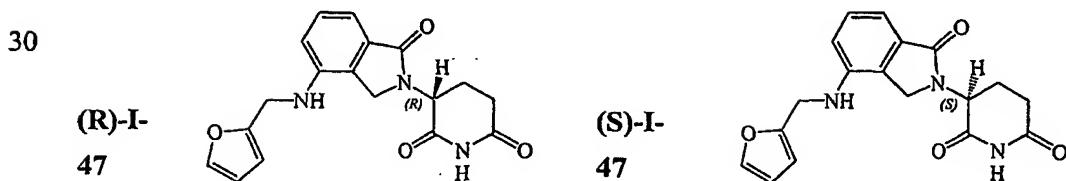
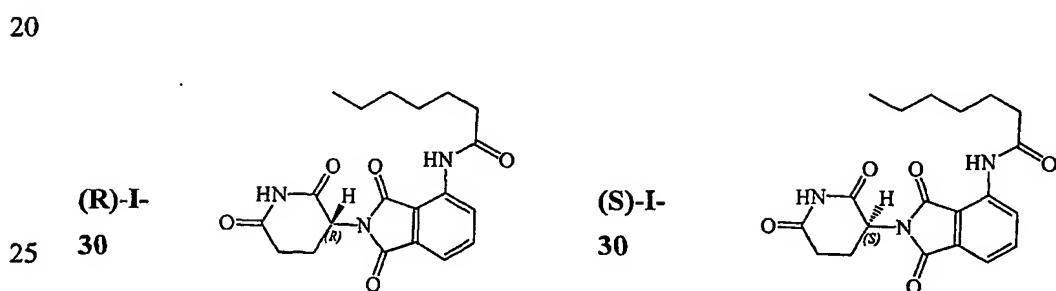
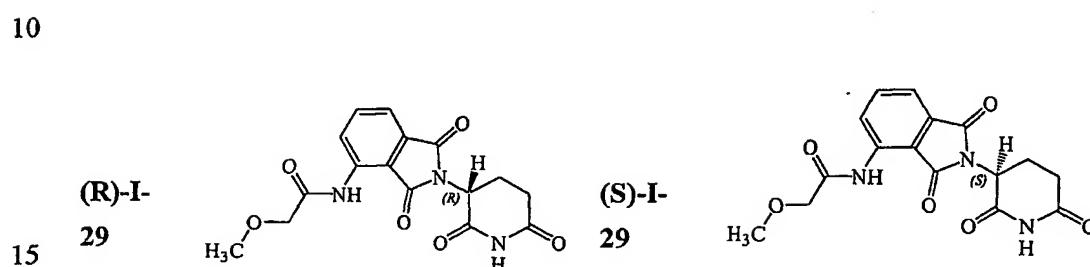
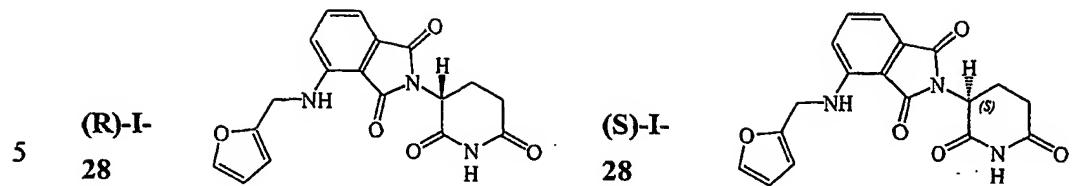
Examples of optically or enantiomerically pure stereoisomers of the invention are depicted in Table 2 below.

15

TABLE 2: Examples of Stereoisomers of the Invention

No.	Structure	No.	Structure	
20	(R)-I-1		(S)-I-1	
25	(R)-I-3		(S)-I-3	
30				
35				





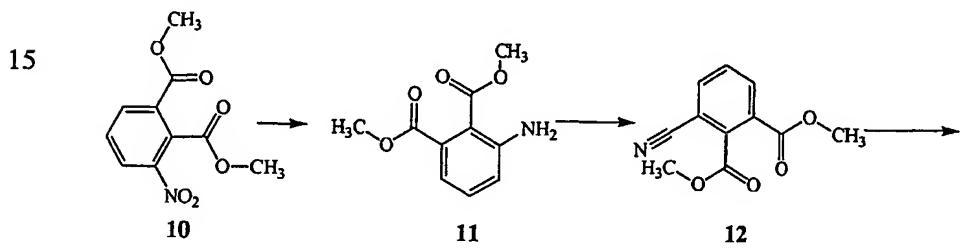
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6.1 Synthesis of the Compounds of the Invention

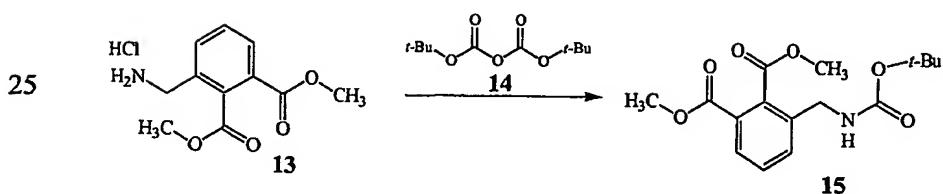
The compounds of the invention can be obtained via standard, synthetic methodology. Some convenient methods are illustrated in Schemes 1-8. Starting materials useful for preparing the compounds of the invention and intermediates therefor, are
 5 commercially available or can be prepared from commercially available materials using known synthetic methods and reagents. Such starting materials include, but are not limited to, methyl-2-(methoxycarbonyl)-3-nitrobenzoate; methyl-3-aminomethyl-2-(methoxycarbonyl)benzoate; substituted and unsubstituted aminoglutamide hydrochloride; di-*t*-butyl dicarbonate; and cyclopropylcarbonyl chloride.

10

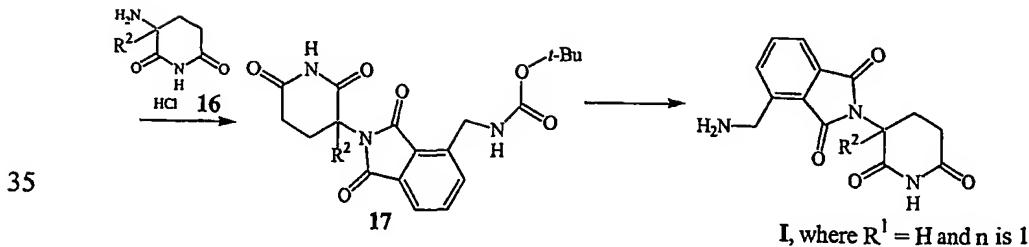
Scheme 1: Synthesis of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (Formula I, wherein R¹ is H and n is 1)



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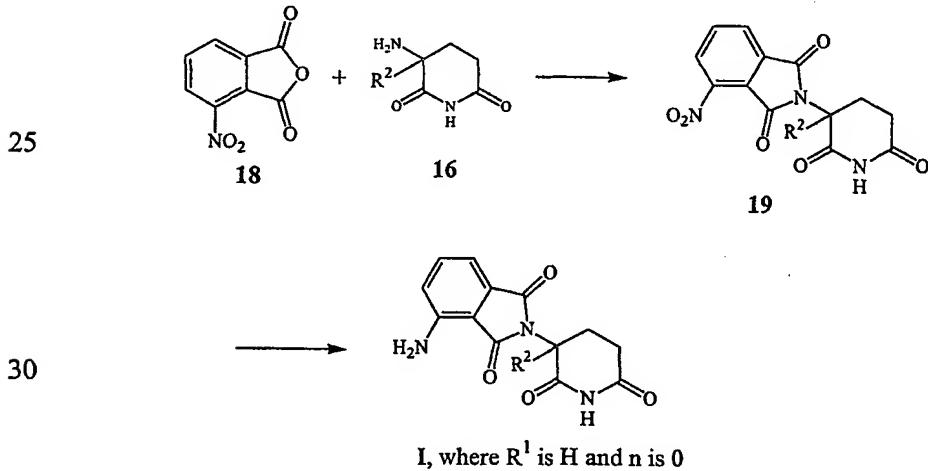


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Scheme 1 outlines one method to synthesize 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (**I**, wherein R¹ is H and n is 1) from compound **10**. In the first step, reduction of **10** (commercially available), for example, with palladium on charcoal and 50 psi of hydrogen, followed by standard isolation and purification gives arylamine **11**. Arylamine **11** converts to nitrile **12** by diazonium salt formation effected by treatment with sodium nitrate then displacement of nitrogen with cyanide according to the classic Sandmeyer procedure. Reduction of nitrile **12**, for example, with palladium on carbon in methanol/aqueous hydrochloric acid under an atmosphere of hydrogen, gives the hydrochloride salt of compound **13**. Treatment of **13** with triethylamine liberates the free base, which in turn reacts with di-*t*-butyl dicarbonate (**14**) (commercially available, for example, from Aldrich Chemical Co. Milwaukee, WI) giving carbamate **15**. Treatment of carbamate **15** with **16**, where R² is as defined above, and a base, such as diisopropylethyl amine gives compound **17** that converts to **I**, wherein R¹ is H and n is 1 upon standard hydrolysis, for example, with aqueous hydrochloric acid/dioxane. Compounds **16** can be obtained by cyclizing the appropriately substituted, amino-protected glutamine by well-known methods (e.g., see WO 98/54170, incorporated herein by reference).

**Scheme 2: Synthesis of 4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione
(Formula I, wherein R¹ is H and n is 0)**

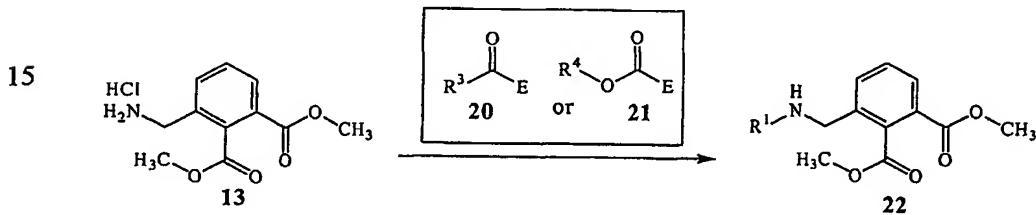


Scheme 2 outlines a convenient method to synthesize 4-amino-2-(2,6-dioxo-3-piperidin-3-yl)-isoindole-1,3-dione (**I**, wherein R¹ is H and n is 0) from 4-nitrophthalic

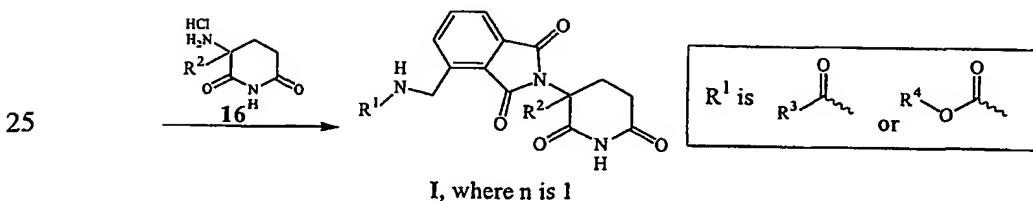
anhydride (18). In the first step, a mixture of 18 and 16 in an acidic medium (*e.g.*, sodium acetate in glacial acetic acid) is heated at about 60 °C to about 150 °C for a time of about 1 hour to about 24 hours, until the reaction is substantially complete. After an aqueous workup, 19 is isolated and characterized according to standard methods (*see e.g.*, United States Patent No. 5,635,517, incorporated herein by reference). Alternately, the reaction may be carried out in other solvents, including pyridine. Conversion of 19 to I, wherein R¹ is H and n is 0, is accomplished by standard hydrogen reduction, for example, with palladium on carbon under about 50 psi to 200 psi of hydrogen at about room temperature to about 100 °C (*see e.g.*, the procedure recited in United States Patent 5,635,517).

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Scheme 3: Synthesis of Compounds of Formula I, wherein R¹ is C(O)R³ or C(O)OR⁴



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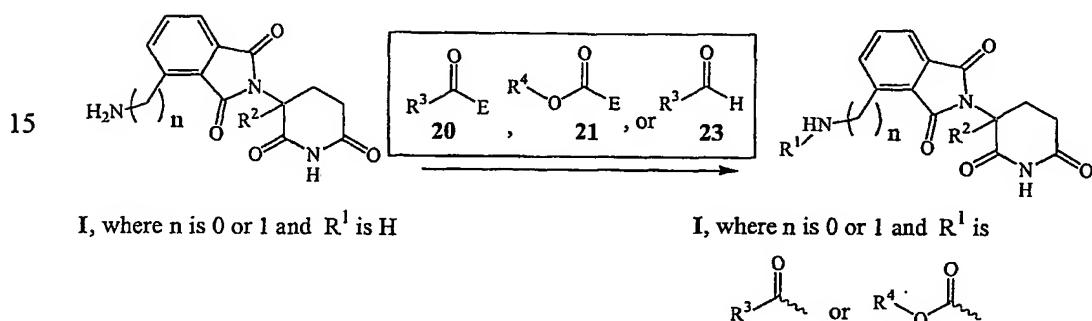
30 Scheme 3 outlines a convenient synthesis of compounds of Formula I, wherein R¹ is C(O)R³ or C(O)OR⁴. In the first step, compound 13, as prepared as in Scheme 1 above, reacts with a compounds 20 or 21, depending on whether R¹ of C(O)R³ or C(O)OR⁴ is desired, to give compounds 22. According to scheme 3, E is a suitable leaving group, for example, but not limited to halides, such as chloride, bromide, and iodide; azido (N₃); arylsulfonyloxy or alkylsulfonyloxy (*e.g.*, tosyloxy or mesyloxy); phenoxy; alkoxy; and oxycarbonyl groups. Preferably, E is a halide, more preferably, chloride. Preferably,

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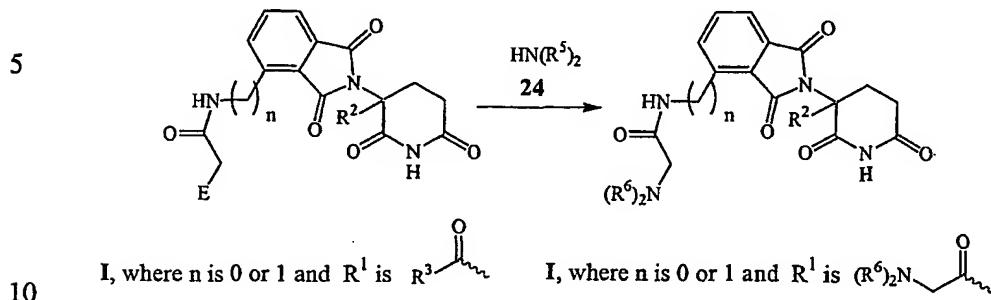
compounds 20 are acid chlorides, such as acetyl chloride and cyclopropylcarbonyl chloride and compounds 21 are chloroformates, such as ethylchloroformate or benzylchloroformate. The reaction is carried out according to standard, well-known procedures, e.g. see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp.417-
 5 419, incorporated herein by reference. Treatment of 22 with 16 using the same procedure as outlined in Scheme 1 gives compounds of Formula I, wherein R¹ is C(O)R³ or C(O)OR⁴.

Scheme 4: Alternative Synthesis of Compounds of Formula I, wherein

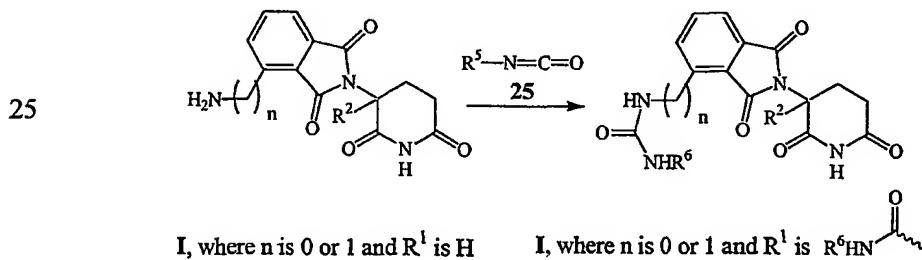
R^1 is $C(O)R^3$ or $C(O)OR^4$



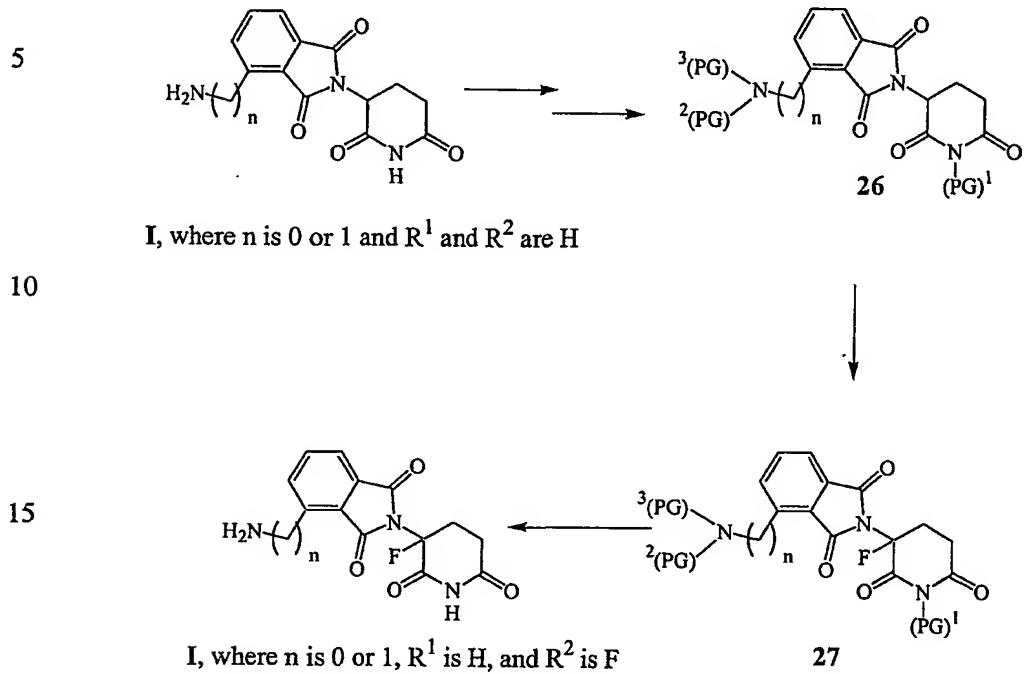
Scheme 4 outlines an alternative synthesis of compounds of Formula I, wherein R¹ is C(O)R³ or C(O)OR⁴ and a convenient synthesis of compounds of Formula I, wherein R¹ is CH₂R³. In the first step, compounds I, wherein R¹ is H, as prepared as in Scheme 1 (n = 1) or Scheme 2 (n = 0) above, reacts with a compounds 20, 21, or 23 depending on whether R¹ of C(O)R³, C(O)OR⁴, or CH₂R³ is desired, to give compounds I where R¹ is C(O)R³, C(O)OR⁴, or CH₂R³. As defined above for Scheme 3, E is a suitable leaving group. Preferably, E is a halide, more preferably, chloride. Preferably, compounds 20 are acid chlorides, such as chloroacetyl chloride and *t*-butylacetyl chloride. Aldehydes 23 are readily available commercially or synthesized by well-known methods. The reaction of 20 or 21 with I, where R¹ is H is carried out according to standard, well-known procedures for nucleophilic displacement, e.g. see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp.417-419. The reaction of 23 with I, where R¹ is H is accomplished according to the well-known reductive-amination procedure between an aldehyde and a primary amine, e.g. see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp.898-902, incorporated herein by reference.

Scheme 5: Synthesis of Compounds of Formula I, wherein R¹ is C(O)CH₂N(R⁶)₂

Scheme 5 outlines one method for the synthesis of compounds of Formula I, wherein R¹ is C(O)CH₂N(R⁶)₂. A compound of Formula I, wherein R¹ is C(O)R³ and R³ is (CH₂)E, where E is a suitable leaving group as defined for Scheme 3, reacts with amines 24 to give the desired Formula I compound, where R¹ is C(O)CH₂N(R⁶)₂. Preferably, E is 15 chloro and R⁵ is (C₁-C₈)alkyl, such as methyl. The reaction is performed according to standard, well-known procedures, e.g. see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 411-413, incorporated herein by reference.

Scheme 6: Synthesis of Compounds of Formula I, wherein R¹ is C(O)NHR⁵

30 Scheme 6 shows one method to synthesize compounds of Formula I, wherein R¹ is C(O)NHR⁵. A compound of Formula I, where R¹ is H reacts with isocyanates 25 under routine conditions to give a compound I, where R¹ is C(O)NHR⁵. The reaction is performed according to standard, well-known procedures, e.g. see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 903, 35 incorporated herein by reference.

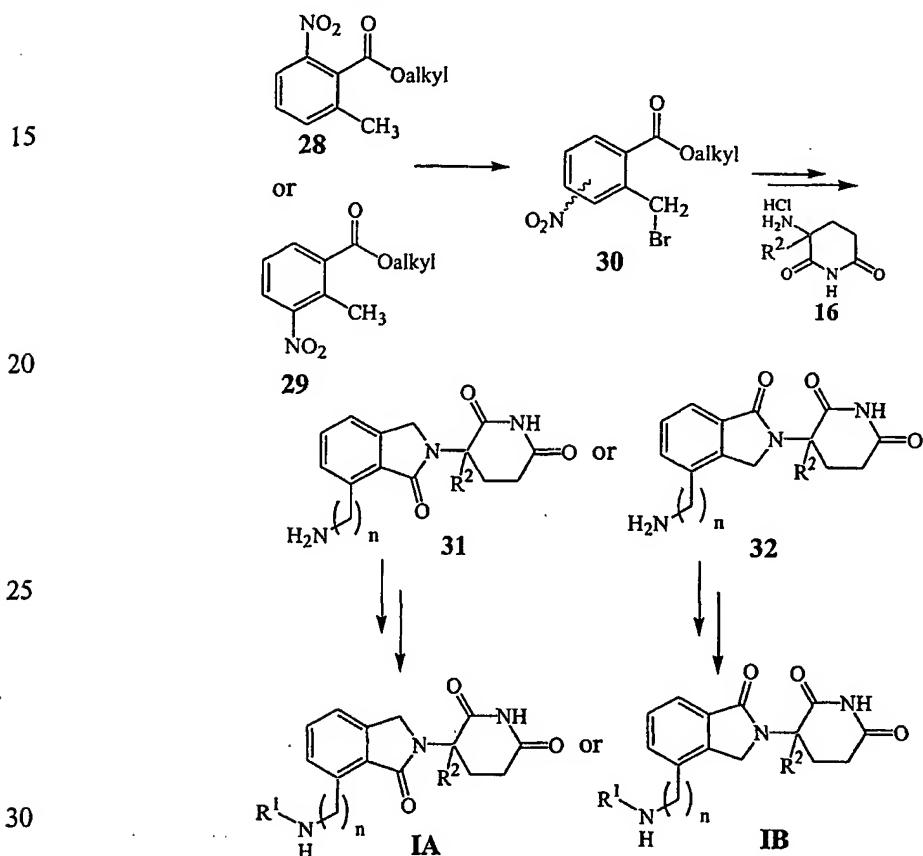
Scheme 7: Synthesis of Compounds of Formula I, wherein R² is F

Scheme 7 shows one method to synthesize compounds of Formula I, wherein R² is F. A similar method is described in U.S. Patent No. 5,874,448, incorporated herein by reference. In the first step, compounds of Formula I, where R¹ and R² are H are first protected with suitable nitrogen-protecting groups (PG¹, PG², and PG³) at the methyleneamino and glutarimide nitrogens, respectively, to give compounds 26. As used herein, a "nitrogen protecting group" means a group that is reversibly attached to the nitrogen that renders the nitrogen moiety unreactive during a subsequent reaction(s) and that can be selectively cleaved to regenerate the original nitrogen moiety once its protecting purpose has been served. Examples of suitable protecting groups are found in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 494-654 (1999), incorporated by reference, and United States Patent No. 5,874,448. Preferably, the nitrogen-protecting group is stable in a basic reaction medium but can be cleaved by acid. Preferably, all of PG¹, PG², and PG³ protecting groups are *tert*-butyloxycarbonyl, attached by treatment of compounds of Formula I, where R¹ and R² are H with in excess of 3 equivalents of di-*tert*-butyl carbonate as described in United States Patent No. 5,874,448. The fluorination-reaction procedure, to give compounds 27, is described in detail in United

States Patent No. 5,874,448 and can be effected by treating deprotonated **26** with a variety of reagents, such as *N*-fluorobenzenesulfonimide, perchloryl fluoride, or *N*-fluorobenzene-disulfonimide. Deprotonated **26** can be prepared by treatment of **26** with strong base, such as *n*-butyl lithium, sodium bis(trimethylsilyl)amide, sodium hydride, or lithium diisopropylamide. Deprotection of compounds **27** to give compounds **I**, where R¹ is H and R² is F is effected by standard procedures such as those described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 494-654 (1999) and United States Patent No. 5,874,448.

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Scheme 8: Synthesis of Compounds of Formula I, wherein one of
one of X and Y is C=O and the other is CH₂,



compounds **I**, where n is 0 or 1 and one of X and Y is C=O and the other is CH₂

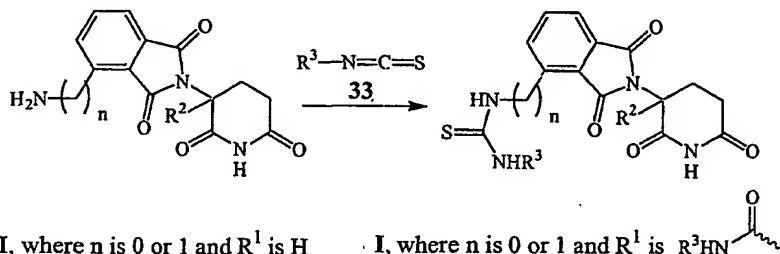
Scheme 8 depicts convenient general synthetic methodology to prepare compounds **I**, where one of X and Y is C=O and the other is CH₂ (*i.e.*, compounds **IA** and **IB**).

IB). In compounds **IA**, the isoindolin-ring carbonyl is *cis* with respect to the methyleneamino ($n = 1$) or the amino ($n = 0$) group, conversely, in compounds **IB**, the isoindolin-ring carbonyl is *trans*. In one convenient methods, compounds **IA** and **IB** can be prepared starting from compounds **28** or **29** respectively, for example, using the
 5 methodology described in WO 98/54170, incorporated herein by reference. Compounds **28** and compounds **29** are available commercially or readily available through well-known synthetic methodology. For example, methyl-2-methyl-3-nitrobenzoate (**29**, where alkyl is methyl) is commercially available from Aldrich Chemical Co., Milwaukee, WI.
 Compounds **28** and **29** are first brominated at the activated benzylic position with a
 10 brominating agent such as *N*-bromosuccinimide under the influence of light or other radical initiator to yield methylbromo-compounds **30**. Exemplary brominating procedures are reviewed in March, *J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 694-697, incorporated herein by reference. Compounds **30** are then converted into compounds **31** or **32** and thereafter to **IA** or **IB** by adapting the synthetic
 15 methods presented in Schemes 1 to 5 above, including standard cyclization with compounds
16.

Scheme 9: Synthesis of Compounds of Formula I, wherein R¹ is C(S)NHR³

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Scheme 9 shows one method to synthesize compounds of Formula I, wherein R¹ is C(S)NHR³. A compound of Formula I, where R¹ is H reacts with isothiocyanates **28** under routine conditions to give a compounds I, where R¹ is C(O)NHR⁵. The reaction is performed according to standard, well-known procedures, e.g. see March, *J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 903, incorporated herein by reference.

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7. Therapeutic Uses of Compounds or Compositions of the Invention

In accordance with the invention, a compound or composition of the invention is administered to a mammal, preferably, a human, with or at risk of a disease or medical condition, for example, cancer, such as solid tumors and blood-born tumors. Specific examples of cancers treatable or preventable by administering compounds of the invention include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectal; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are particularly useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias.

The compounds of the invention are also useful to treat or prevent heart disease, such as congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

The compounds of the invention can also be used to treat or prevent viral, genetic, inflammatory, allergic, and autoimmune diseases. For example, the compounds are useful to treat or prevent diseases including, but not limited to, HIV; hepatitis; adult respiratory distress syndrome; bone-resorption diseases; chronic pulmonary inflammatory diseases; dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis, Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; ENL in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

The compounds of the invention are also useful for treating or preventing bacterial infections including, but not limited to, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to an amelioration of at least one measurable physical parameter, not necessarily discernible by the mammal. In yet another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of

a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder.

In certain embodiments, the compounds of the invention or the compositions of the invention are administered to a mammal, preferably, a human, as a prophylactic. As used 5 herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. In a preferred mode of the embodiment, the compounds and compositions of the present invention are administered as a preventative measure to a mammal, preferably, a human, having a genetic or non-genetic predisposition to a medical condition, for example, cancers, such as solid tumors and blood-born tumors. Specific 10 examples of cancers preventable by compounds of the invention include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectal; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are particularly useful for treating cancers of the 15 blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias.

The compounds of the invention are also useful for preventing heart disease, such as congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

20 The compounds of the invention can also be used to prevent viral, genetic, inflammatory, allergic, and autoimmune diseases. For example, the compounds are useful to prevent diseases including, but not limited to, HIV; hepatitis; adult respiratory distress syndrome; bone-resorption diseases; chronic pulmonary inflammatory diseases; dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis 25 syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis, Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythematosus; ENL in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

30 The compounds of the invention are also useful for preventing bacterial infections or symptoms including, but not limited to, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

8. Therapeutic/Prophylactic Administration of The Compounds and Compositions of The Invention

Due to the activity of the compounds and compositions of the invention, they are useful in veterinary and human medicine. The invention provides methods of treatment and prevention by administration of a therapeutically effective amount of a compound or a composition of the invention to a mammal, preferably, a human. The term "mammal" as used herein, encompasses any mammal. Preferably a mammal is in need of such treatment or prevention. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys, etc., more preferably, a human.

10 Administration of compounds of the invention can be systemic or local. In most instances, administration to a mammal will result in systemic release of the compounds of the invention (*i.e.*, into the bloodstream). Methods of administration include enteral routes, such as oral, buccal, sublingual, and rectal; topical administration, such as transdermal and intradermal; and parenteral administration. Suitable parenteral routes include injection via a hypodermic needle or catheter, for example, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intraarterial, intraventricular, intrathecal, and intracameral injection and non-injection routes, such as intravaginal rectal, or nasal administration. Preferably, the compounds and compositions of the invention are administered orally. In specific embodiments, it may be desirable to administer one or more compounds of the invention locally to the area in need of treatment. This may be achieved, for example, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

15 The compounds of the invention can be administered via typical as well as non-standard delivery systems, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, etc. For example, the compounds and compositions of the invention can be delivered in a vesicle, in particular a liposome (*see* Langer, 1990, *Science* 249:1527-1533; Treat *et al.*, in *Liposomes in Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; *see generally ibid.*). In another example, the compounds and compositions of the invention can be delivered in a controlled release system. In one embodiment, a pump may be used (*see* Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald *et al.*, 1980, *Surgery* 88:507 Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another example, polymeric materials can be used (*see* Medical Applications of Controlled Release, Langer

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- and Wise (eds.), CRC Press., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; *see also* Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 71:105). In still another example, a controlled-release system can be placed in proximity of the target area to be treated, *e.g.*, the liver, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, in *Medical Applications of Controlled Release, supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, *Science* 249:1527-1533) can be used.
- 10 When administered as a composition, a compound of the invention will be formulated with a suitable amount of a pharmaceutically acceptable vehicle or carrier so as to provide the form for proper administration to the mammal. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the invention is formulated for administration to a mammal. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. Preferably, when administered to a mammal, the compounds and compositions of the invention and pharmaceutically acceptable vehicles, excipients, or diluents are sterile. An aqueous medium is a preferred vehicle when the compound of the invention is administered intravenously, such as water, saline solutions, and aqueous dextrose and glycerol solutions.
- 15 The present compounds and compositions can take the form of capsules, tablets, pills, pellets, lozenges, powders, granules, syrups, elixirs, solutions, suspensions, emulsions, suppositories, or sustained-release formulations thereof, or any other form suitable for administration to a mammal. In a preferred embodiment, the compounds and compositions of the invention are formulated for administration in accordance with routine procedures as a pharmaceutical composition adapted for oral or intravenous administration to humans. In one embodiment, the pharmaceutically acceptable vehicle is a hard gelatin capsule.
- 20 Examples of suitable pharmaceutical vehicles and methods for formulation thereof are described in *Remington: The Science and Practice of Pharmacy*, Alfonso R. Gennaro ed.,
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Mack Publishing Co. Easton, PA, 19th ed., 1995, Chapters 86, 87, 88, 91, and 92, incorporated herein by reference.

Compounds and compositions of the invention formulated for oral delivery, are preferably in the form of capsules, tablets, pills, or any compressed pharmaceutical form.

- 5 Moreover, where in tablet or pill form, the compounds and compositions may be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds and compositions of the invention. In these later platforms, fluid from the environment
- 10 surrounding the capsule is imbibed by the driving compound that swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles, excipients, and diluents,
- 15 such as magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents, such as talc, magnesium stearate, mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and
- 20 propylhydroxybenzoates. Such vehicles are preferably of pharmaceutical grade. Orally administered compounds and compositions of the invention can optionally include one or more sweetening agents, such as fructose, aspartame or saccharin; one or more flavoring agents such as peppermint, oil of wintergreen, or cherry; or one or more coloring agents to provide a pharmaceutically palatable preparation.
- 25 A therapeutically effective dosage regimen for the treatment of a particular disorder or condition will depend on its nature and severity, and can be determined by standard clinical techniques according to the judgment of a medical practitioner. In addition, *in vitro* or *in vivo* assays can be used to help identify optimal dosages. Of course, the amount of a compound of the invention that constitutes a therapeutically effective dose also depends on
- 30 the administration route. In general, suitable dosage ranges for oral administration are about 0.001 milligrams to about 20 milligrams of a compound of the invention per kilogram body weight per day, preferably, about 0.7 milligrams to about 6 milligrams, more preferably, about 1.5 milligrams to about 4.5 milligrams. In a preferred embodiment, a mammal, preferably, a human is orally administered about 0.01 mg to about 1000 mg of a compound
- 35 of the invention per day, more preferably, about 0.1 mg to about 300 mg per day, or about 1

mg to about 250 mg in single or divided doses. The dosage amounts described herein refer to total amounts administered; that is, if more than one compound of the invention is administered, the preferred dosages correspond to the total amount of the compounds of the invention administered. Oral compositions preferably contain 10% to 95% of a compound 5 of the invention by weight. Preferred unit oral-dosage forms include pills, tablets, and capsules, more preferably capsules. Typically such unit-dosage forms will contain about 0.01 mg, 0.1 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, 250 mg, or 500 mg of a compound of the invention, preferably, from about 5 mg to about 200 mg of compound per unit dosage.

10 In another embodiment, the compounds and compositions of the invention can be administered parenterally (e.g., by intramuscular, intrathecal, intravenous, and intraarterial routes), preferably, intravenously. Typically, compounds and compositions of the invention for intravenous administration are solutions in sterile isotonic aqueous vehicles, such as water, saline, Ringer's solution, or dextrose solution. Where necessary, the compositions 15 may also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. For intravenous administration, the compounds and compositions of the invention can be supplied as a sterile, dry lyophilized powder or water-free concentrate in a hermetically sealed container, such as an ampule or sachette, the container indicating the 20 quantity of active agent. Such a powder or concentrate is then diluted with an appropriate aqueous medium prior to intravenous administration. An ampule of sterile water, saline solution, or other appropriate aqueous medium can be provided with the powder or concentrate for dilution prior to administration. Or the compositions can be supplied in pre-mixed form, ready for administration. Where a compound or composition of the invention 25 is to be administered by intravenous infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical-grade water, saline, or other suitable medium.

Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter, modified vegetable oils, and other fatty 30 bases. Suppositories can be formulated by well-known methods using well-known formulations, for example see *Remington: The Science and Practice of Pharmacy*, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, PA, 19th ed., 1995, pp. 1591-1597, incorporated herein by reference

To formulate and administer topical dosage forms, well-known transdermal and 35 intradermal delivery mediums such as lotions, creams, and ointments and transdermal

delivery devices such as patches can be used (Ghosh, T.K.; Pfister, W.R.; Yum, S.I. *Transdermal and Topical Drug Delivery Systems*, Interpharm Press, Inc. p. 249-297, incorporated herein by reference). For example, a reservoir type patch design can comprise a backing film coated with an adhesive, and a reservoir compartment comprising a 5 compound or composition of the invention, that is separated from the skin by a semipermeable membrane (e.g., U.S. Patent 4,615,699, incorporated herein by reference). The adhesive coated backing layer extends around the reservoir's boundaries to provide a concentric seal with the skin and hold the reservoir adjacent to the skin.

The invention also provides pharmaceutical packs or kits comprising one or more 10 containers filled with one or more compounds of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In one embodiment, the kit contains more than one compound of the invention. In another 15 embodiment, the kit comprises a compound of the invention and another biologically active agent.

The compounds of the invention are preferably assayed *in vitro* and *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific compound of the 20 invention or a combination of compounds of the invention is preferred. The compounds and compositions of the invention may also be demonstrated to be effective and safe using animal model systems. Other methods will be known to the skilled artisan and are within the scope of the invention.

25 8.1 Combination Therapy

In certain embodiments, a compound of the invention is administered to a mammal, preferably, a human concurrently with one or more other biologically active agents, or with one or more other compounds of the invention, or with both. By "concurrently" it is meant that a compound of the invention and the other agent are administered to a mammal in a 30 sequence and within a time interval such that the compound of the invention can act together with the other agent to provide an increased or synergistic benefit than if they were administered otherwise. For example, each component may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently closely in time so as to provide the 35 desired treatment effect. Preferably, all components are administered at the same time, and

if not administered at the same time, preferably, they are all administered from about 6 hours to about 12 hours apart from one another.

When used in combination with other therapeutic agents, the compounds of the invention and the therapeutic agent can act additively or, more preferably, synergistically.

- 5 In one embodiment, a compound or a composition of the invention is administered concurrently with another therapeutic agent in the same pharmaceutical composition. In another embodiment, a compound or a composition of the invention is administered concurrently with another therapeutic agent in separate pharmaceutical compositions. In still another embodiment, a compound or a composition of the invention is administered
- 10 prior or subsequent to administration of another therapeutic agent. As many of the disorders for which the compounds and compositions of the invention are useful in treating are chronic disorders, in one embodiment combination therapy involves alternating between administering a compound or a composition of the invention and a pharmaceutical composition comprising another therapeutic agent, *e.g.*, to minimize the toxicity associated
- 15 with a particular drug. In certain embodiments, when a composition of the invention is administered concurrently with another therapeutic agent that potentially produces adverse side effects including, but not limited to toxicity, the therapeutic agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.
- 20 The present compounds and compositions can be administered together with hormonal and steroidal anti-inflammatory agents, such as, estradiol, conjugated estrogens (*e.g.*, PREMARIN, PREMPRO, AND PREMPHASE), 17 beta estradiol, calcitonin-salmon, levothyroxine, dexamethasone, medroxyprogesterone, prednisone, cortisone, flunisolide, and hydrocortisone; non-steroidal anti-inflammatory agents, such as tramadol, fentanyl,
- 25 metamizole, ketoprofen, naproxen, nabumetone, ketorolac, tromethamine, loxoprofen, ibuprofen, aspirin, and acetaminophen; anti-TNF- α antibodies, such as infliximab (REMICADETM) and etanercept (ENBRELTM); AIDS and AIDS-related therapies, such as lamivudine, zidovudine, indinavir sulfate, stavudine, and lamivudine; chemotherapeutics and cancer-related therapies, such as anti-angiogenesis agents, topoisomerase inhibitors,
- 30 alkylating agents, nitrogen mustards, antibiotics such as doxorubicin, and paclitaxel, cisplatin, tamoxifen, docetaxel, irinotecan, temozolamide, thalidomide, amino-thalidomide, amino-EM-12, epirubicin, leuprolide, bicalutamide, goserelin implant, gemcitabine, sargramostim anti-cancer antibodies, such as Rituxan, and anti-cancer vaccines, such as Theratope and HSPPC-96; antibiotics, such as amoxicillin, ampicillin sodium, cefaclor, and
- 35 ciprofloxacin; dermatological therapeutics, such as isotretinoin, clindamycin phosphate

topical; antiarthritic therapies, such as diclofenac sodium, nabumetone, misoprostol, and rofecoxib; immunosuppressive therapies, such as cyclosporine, FK506, mycophenolate mofetil, and methylprednisolone; multiple sclerosis therapies, such as interferon beta-1a, interferon beta-1b, and glatiramer; osteoporosis therapies, such as vitamin K₂; cystic fibrosis 5 therapies, such as dornase alpha and tobramycin; and Alzheimer's disease therapies, such as dolasetron mesylate, and donepezil hydrochloride.

In one embodiment of the invention, the compounds of the invention can be used, not only to directly treat the disorder, but also to reduce the dose or toxicity of another chemotherapeutic. For example, the compounds of the invention can be administered to 10 reduce gastrointestinal toxicity associated with a topoisomerase inhibitor, such as irinotecan.

8.2 Assays

The compounds of the invention can be assayed for their ability to modulate the 15 production of TNF- α by well-known methods in the art, *see e.g.*, Corral *et al.*, 1999, *J. Immun.* 163:380-386 and Muller *et al.*, 1996, *J. Med. Chem.* 39:3238 (assay for the inhibition of production of TNF- α) and Muller *et al.*, 1998, *Bioorg. Med. Chem. Lett.* 8:2669, all three of which citations are incorporated herein by reference.

20 **8.2.1 Assay For The Ability of a Compound of The Invention to Modulate the Production of TNF- α**

PBMC cells—normal human donors—were obtained by Ficoll-Hypaque density centrifugation (Pharmacia Fine Chemicals, Piscataway, NJ). The cells (about 2×10^5 to 10^6 cells/ml) are cultured with RPMI (commercially available, *e.g.*, from Gibco Laboratories, 25 Grand Island, NY) supplemented with 10AB+ serum (commercially available, *e.g.*, from Biocell, Rancho Dominguez, CA), about 2 mM L-glutamine, about 100 U/ml penicillin, and about 100 μ g/ml streptomycin (Gibco). The test compounds are dissolved in DMSO at 20 mg/ml, further dilution can be done with culture medium. The final DMSO concentration in all samples including the controls should be about 0.25% by weight. Test compounds 30 were added to cells 1 hour prior to the addition of LPS. The PBMC cells, in triplicate, are stimulated by 1 μ g/ml LPS from *Salmonella* Minnesota R595 (List Biological Labs, Campbell, CA) and incubated for about 18 to about 20 hours at 37 °C (5% CO₂) in 96-well flat-bottom polystyrene Costar tissue culture plates (Corning, Corning, NY) for the induction of TNF- α . Cells are incubated with or without compounds of the invention 35 (negative controls). The supernatants are collected for the determination of cytokine levels by ELISA (Endogen, Cambridge, MA). Percent inhibition can be determined as $100 \times [1 -$

(TNF- α EXPERIMENTAL/ TNF- α CONTROL)]. Assays are performed, in accordance with the assay kit's manufacturer, in 96-well plates (Nunc Immunoplates, Roskilde, Denmark) coated with the affinity-purified rabbit anti-TNF- α antibody (0.5 μ g/ml; 12-16 hours; 4 °C) and blocked for 2 hours at room temperature with PBS/0.05% Tween 20 (Sigma Chemical Co., St. Louis, Mo.) containing 5 mg/ml BSA. After washing, 100 μ l of TNF- α standards, samples and controls are applied to the wells, and the plates are incubated for 12-24 hours at 4 °C. After the incubation, plates are washed and a second antibody, horseradish peroxidase (HRP)-conjugated mouse monoclonal anti-TNF- α , diluted 1:2,000 in PBS/BSA/Tween, is applied to the wells, after which they incubated for 2 hours at room temperature. The color reaction is developed with the OPD substrate (0.4 mg/ml o-phenylenediamine [Sigma Chemical Co.] in 24 mM citric acid, 51 mM sodium phosphate, pH 5.0 [phosphate-citrate buffer: Sigma Chemical Co.] containing 0.012% hydrogen peroxide [Fisher Scientific Co., Pittsburgh, PA.]) and absorbance read at 492 nm in an automated ELISA reader (Dynatech Laboratories, Inc., Alexandria, Va.).

15

8.2.2 Assay For T-Cell Stimulation and IL-2 Stimulation:
PMC Stimulation by Anti-CD3 Ab

PBMC (1×10^6 cells) are stimulated by cross-linking of the TCR by immobilized monoclonal mouse anti-human CD3 (Orthoclone OKT3) as described in Haslett *et al.*, 20 1998, *J. Exp. Med.* 187:1885, incorporated herein by reference. The anti-CD3 Ab is diluted to 10 μ g/ml in 100 μ l PBS and coated onto 48-well flat-bottom polystyrene Falcon tissue culture plates (Becton Dickinson, Franklyn Lakes, NJ) by overnight incubation at 4°C. Appropriate dilutions of compounds of the invention are added at the start of the cell culture. Supernatants are collected at 24, 43, and 72 hours and assayed for TNF- α levels. 25 Cells are collected at 48 hours for evaluation of CD40 ligand (CD40L)³ and CD3 surface expression by two-color flow cytometry (anti-CD40L, PharMingen, San Diego, CA; anti-CD3, Becton Dickinson, San Jose, CA).

8.2.3 Assay For the Modulation of Production of IL-1 β and IL-10

30 This assay can be performed according to the procedure outlined in Muller *et. al.*, 1999, *J. Immunol.* 176, 380, hereby expressly incorporated herein by reference. PMBC (2×10^5 cells) incubated in 96-well flat-bottom polystyrene Costar tissue culture plates (Corning, Corning, NY) were stimulated by 1 mg/ml LPS from Salmonella minnesota R595 (List Biological Labs, Campbell, CA) for the induction of IL-1 β , and IL-10. Cells 35 were incubated with or without thalidomide or analogues for 20 h, and culture supernatants

were collected and frozen immediately at - 70 °C until assayed in triplicate or duplicate. IL-1 β and IL-10 levels were measured by ELISA (Endogen, Cambridge, MA) as described by the manufacturer.

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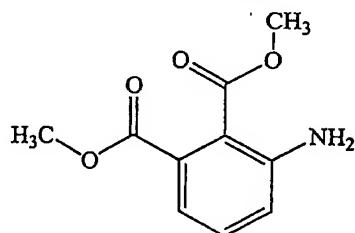
9. Examples of Syntheses of Compounds of the Invention

The following Examples further illustrate methods for synthesizing compounds and intermediates of the invention. It is to be understood that the invention is not limited to the specific details of the Examples set forth below.

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Methyl-3-amino-2-(methoxycarbonyl)benzoate

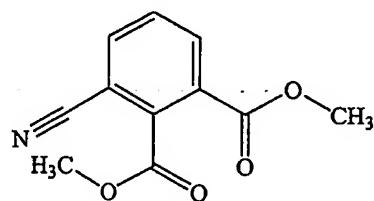
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Methyl-3-cyano-2-(methoxycarbonyl)benzoate

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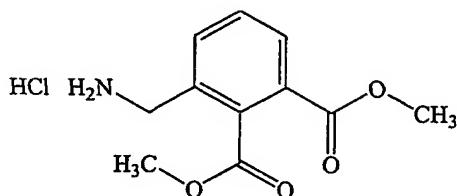


To a stirred suspension of methyl-3-amino-2-(methoxycarbonyl)benzoate (17.0 g, 81 mmol) in a mixture of concentrated HCl (44 ml) and water (440 ml) at 4 °C was added a

solution of NaNO₂ (6.73 g, 97 mmol) in water (25 ml) dropwise at 4-5 °C. Stirring was continued for 30 min at 4 °C. The mixture was then carefully neutralized with sat. sodium carbonate to pH 6. A stirred solution of CuCN (9.46 g, 105 mmol) and KCN (6.38 g, 105 mmol) in water (150 ml) was warmed to 60 °C. The cold neutralized diazonium solution
 5 was then added in small portions at a time with vigorous stirring. The mixture was stirred at 60 °C for 1 hour and then cooled to room temperature. The mixture was extracted with dichloromethane (4 × 150 ml) and the combined dichloromethane extracts were washed with water (2 × 100 ml), brine (100 ml) and dried. The solvent was removed *in vacuo* and the product was purified by chromatography (dichloromethane) to afford 12.36 g (65%) of
 10 the product as a light yellow solid: ¹H NMR (CDCl₃) δ 8.19 (d, J=7.9 Hz, 1H), 7.89 (d, J=7.4 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 4.03 (s, 3H), 3.94 (s, 3H).

Methyl-3-aminomethyl-2-(methoxycarbonyl)benzoate hydrochloride

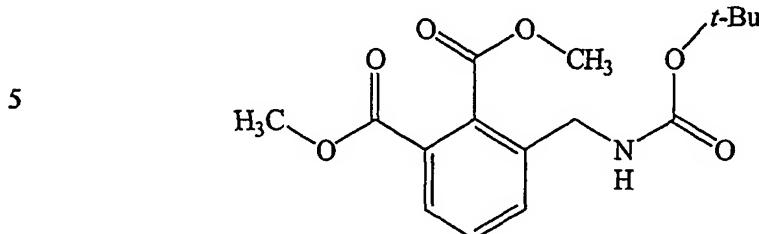
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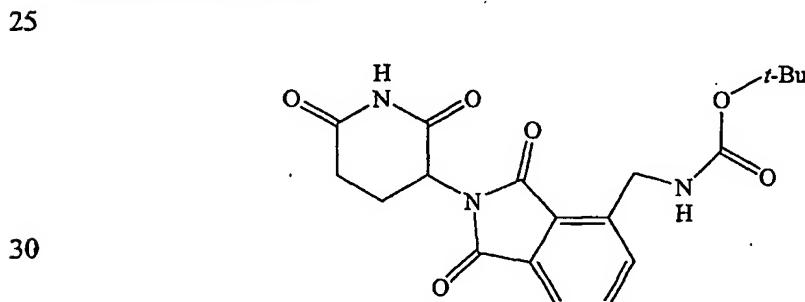
- 20 To a solution of methyl-3-cyano-2-(methoxycarbonyl)benzoate (12.3 g, 57 mmol) in methanol (250 ml) and 4N HCl (40 ml) was added 10% Pd/C (1.2 g). The mixture was hydrogenated under 50 psi of hydrogen in a Parr Type Shaker for 17 hours. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was further evaporated with ethanol (2 × 25 ml) and toluene (25 ml) and dried under vacuum.
 25 The resulting solid was slurried in ether (50 ml) for 1 hour. The slurry was then filtered and dried to give 13.46 g (90%) of the product as a white solid: ¹H NMR (DMSO-d₆) δ 8.79 (b, 2H), 7.94 (d, J=7.8 Hz, 1H), 7.88 (d, J=7.7 Hz, 1H), 7.72 (t, J=7.7 Hz, 1H), 4.03 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H); ¹³C NMR (DMSO-d₆) δ 167.58, 166.12, 133.41, 133.18, 132.28, 130.62, 129.49, 52.99, 52.92, 39.25.

30

35

Methyl-3-[*t*-butoxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate

10 Triethylamine (3.89 g, 38 mmol) was added dropwise to a stirred suspension of methyl-3-aminomethyl-2-(methoxycarbonyl)benzoate hydrochloride (4.0 g, 15 mmol) in dichloromethane (100 ml). The mixture was cooled in an ice bath to 8 °C. A solution of di-*t*-butyl dicarbonate (3.7 g, 16 mmol) in dichloromethane (20 ml) was added dropwise at 8 °C. After the addition was complete, the cooled mixture was stirred for an additional 30 minutes, and then warmed to room temperature for 1 hour. The mixture was washed with water (2 × 40 ml), brine (40 ml) and dried. Solvent was removed *in vacuo* and the product was purified by chromatography (hexane/ethyl acetate 7 to 3) to afford 4.66 g (93%) of the product as an oil: ¹H NMR (CDCl₃) δ 7.87 (d, J=7.4 Hz, 1H), 7.62 (d, J=7.4 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H), 5.16 (b, 1H), 4.30 (d, J=6.1 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 1.42 (s, 9H); ¹³C NMR (CDCl₃) δ 169.41, 166.18, 155.57, 137.09, 134.04, 133.32, 129.76, 128.95, 128.64, 79.52, 52.72, 52.50, 42.23.

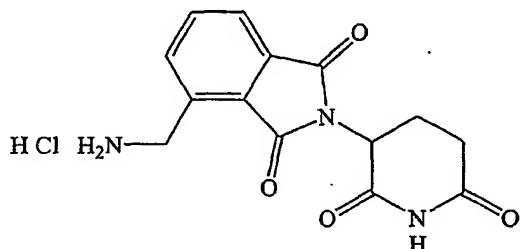
[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl]-carbamic acid *tert*-butyl ester I-1

35 Diisopropylethylamine (3.20 g, 25 mmol) was added to a stirred suspension of methyl-3-[*t*-butoxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate (8.00 g, 25 mmol) and aminoglutaramide hydrochloride (4.07 g, 25 mmol) in DMF (60 ml). The mixture was heated to 120 °C for 24 hours and then cooled to room temperature. The

mixture was poured into cold water (300 ml) and extracted with ethyl acetate (4x100 ml each). The combined ethyl acetate extracts were washed with water (2 x 50 ml), brine (50 ml) and dried. Solvent was removed *in vacuo* and the product purified by flash chromatography (dichloromethane/ethyl acetate 8 to 2) to yield 4.66 g of recovered starting material and 3.31 g (82%) of the product as a white solid: mp 180-182 °C; ¹H NMR (CDCl₃) δ 8.51 (s, 1H), 7.81-7.67 (m, 3H), 5.54 (b, 1H), 5.03-4.96 (dd, J=5.2 and 11.2 Hz, 1H), 4.66 (d, J=6.3 Hz, 2H), 2.95-2.74 (m, 3H), 2.18-2.14 (m, 1H), 1.43 (s, 9H); ¹³C NMR (CDCl₃) δ 170.99, 168.08, 167.95, 167.07, 155.86, 139.17, 135.00, 134.61, 132.15, 128.22, 122.82, 79.81, 49.21, 40.53, 31.33, 28.32, 22.58; Anal. Calcd for C₁₉H₂₁N₃O₆: C, 58.91; H, 5.46; N, 10.85. Found: C, 59.08; H, 5.51; N, 10.69.

4-(Aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione I-2, hydrochloride

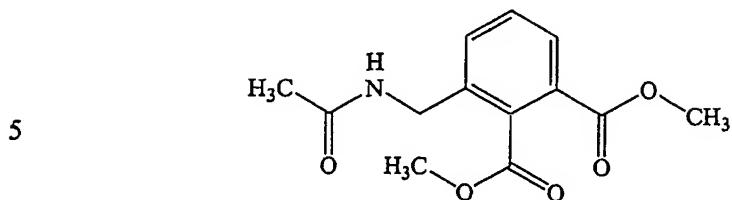
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A solution of 4 N HCl in dioxane (10 ml) was added to a stirred solution of (*t*-butoxy)-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}carboxamide (3.3 g, 8.5 mmol) in dichloromethane (50 ml). The mixture was stirred at room temperature overnight. The resulting slurry was filtered and dried to afford 2.4 g (87%) of the product as a white solid: mp 291-293 °C; ¹H NMR (DMSO-*d*₆) δ 11.18 (s, 1H), 8.77 (b, 2H), 8.06-7.93 (m, 3H), 5.22-5.15 (dd, J=5.1 and 12.6 Hz, 1H), 4.49 (s, 2H), 2.97-2.85 (m, 1H), 2.65-2.51 (m, 2H), 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.86, 169.76, 167.35, 166.71, 135.62, 134.98, 132.80, 131.46, 128.62, 123.57, 49.00, 37.00, 30.95, 22.07; Anal. Calcd for C₁₄H₁₄N₃O₄Cl + 0.22water: C, 51.31; H, 4.44; N, 12.82; Cl, 10.82. Found: C, 51.08; H, 4.36; N, 12.47; Cl, 10.61.

35

3-(Acetylamino-methyl)-phthalic acid dimethyl ester

10 Triethylamine (1.87 g, 18 mmol) was added slowly to a stirred suspension of methyl-3-(aminomethyl)-2-(methoxycarbonyl)benzoate hydrochloride (2.0 g, 8 mmol) in dichloromethane (30 ml). The resulting mixture was cooled in an ice bath to 4 °C. Acetyl chloride (0.73 g, 9 mmol) was added dropwise at a rate such that the temperature stayed between 4-7 °C. After addition was complete, the mixture was stirred in the ice bath for an additional 30 minutes and then allowed to warm to room temperature and maintained for 2 hours. The reaction mixture was washed with water (2 × 30 ml), brine (30 ml) and dried.

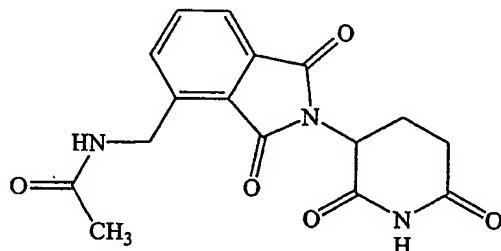
15 Solvent was removed *in vacuo* and the product was purified by chromatography (dichloromethane/ethyl acetate 6 to 4) to afford 1.65 g (80%) of the product as an oil: ¹H NMR (CDCl₃) δ 7.86 (d, J=7.7 Hz, 1H), 7.62 (d, J=7.6 Hz); 7.46 (t, J=7.7 Hz); 6.29 (b, 1H), 4.39 (d, J=6.1 Hz, 2H), 3.93 (s, .3H), 3.90 (s, 3H), 1.96 (s, 3H).

20

N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl]-acetamide I-3

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.93 g, 6 mmol) was added dropwise to a stirred suspension of 3-(acetylamino-methyl)-phthalic acid dimethyl ester (1.61 g, 6.0 mmol) and aminoglutarimide hydrochloride (1.0 g, 6.0 mmol) in DMF (15 ml). The

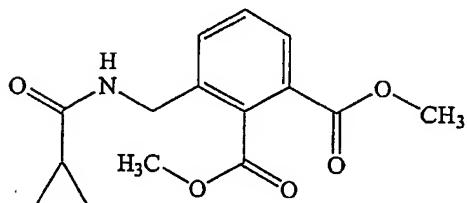
35 mixture was then heated to 120 °C for 24 hours. The cooled mixture was concentrated *in*

vacuo and the residue was stirred with water (25 ml) and dichloromethane (20 ml). The resulting slurry was filtered to give 0.45 g (22%) of the product as a gray solid.

Recrystallization from methanol gave a white solid: mp 177-179 °C; ¹H NMR (DMSO-*d*₆) δ (11.02 (s, 1H), 8.36 (t, J=5.8 Hz, 1H), 7.74-7.55 (m, 3H), 5.05-4.98 (dd, J=5.3 and 12.5 Hz, 1H), 4.57 9D, j=5.9 Hz, 2H), 2.84-2.70 (m, 1H), 2.51-2.34 (m, 2H), 1.95-1.91 (m, 1H), 1.79 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ (172.85, 169.89, 169.81, 167.56, 167.05, 139.37, 134.83, 133.35, 131.58, 127.14, 121.94, 48.91, 37.84, 30.98, 22.54, 22.05; Anal. Calcd. For C₁₆H₁₅N₃O₅ + 0.96 water: C, 55.45; H, 4.92; N, 12.12. Found: C, 55.27; H, 4.82; N, 12.00.

10 Methyl-3-[(cyclopropylcarbonylamino)methyl]-2-(methoxycarbonyl)benzoate

15



Triethylamine (1.87 g, 18 mmol) was added dropwise to a stirred suspension of methyl-3-
20 (aminomethyl)-2-(methoxycarbonyl)benzoate hydrochloride (2.0 g, 7 mmol) in
dichloromethane (40 ml). The mixture was cooled in an ice bath to 4 °C.
Cyclopropylcarbonyl chloride (0.99 g, 9 mmol) was added slowly at 4-8 °C. After addition,
the mixture was stirred in ice bath for 30 min and then warmed to room temperature for 2
hours. The mixture was washed with water (2 × 30 ml), brine (30 ml) and dried. Solvent
25 was removed *in vacuo* and the product was purified by flash chromatography
(dichloromethane/ethyl acetate 9 to 1) to give 2.1 g (93%) of the product as a white solid :
¹H NMR (CDCl₃) (7.87 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.7 Hz, 1H), 7.46 (t, J=7.77 Hz, 1H),
6.31 (m, 1H), 4.43 (d, J=6.0 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 1.36-1.29 (m, 1H), 0.99-
0.93 (m, 2H), 0.76-0.69 (m, 2H).

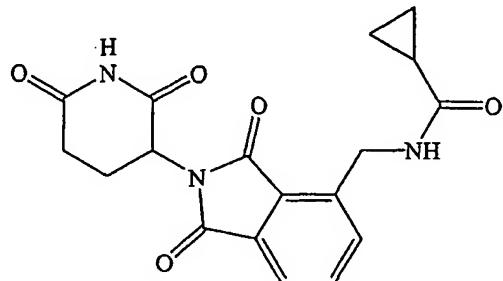
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N-{{[2-(2,6-Dioxo(3-piperidyl)-1,3-dioxoisooindolin-4-yl)methyl]cyclopropyl-carboxamide}
I-4

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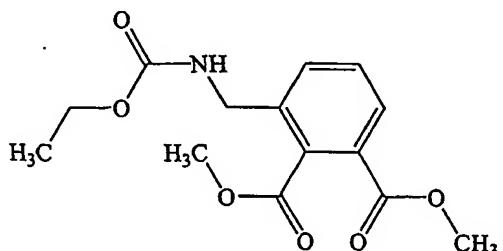


Diisopropylethylamine (0.92 g, 7 mmol) was added to a stirred suspension of methyl-3-[(cyclopropylcarbonylamino)methyl]-2-(methoxycarbonyl)benzoate (2.08 g, 7 mmol) and aminoglutaramide hydrochloride (1.17 g, 7 mmol) in DMF (15 ml). The mixture was heated to 120 °C for 24 hours. The mixture was concentrated *in vacuo* and the residue was stirred with water (40 ml) and ethyl acetate (15 ml). The resulting slurry was filtered to give 0.7 g (27%) of the product as a gray solid. Recrystallization for methanol gave a white solid: mp 240-242 °C; ¹H NMR (DMSO-*d*₆) δ 11.06 (s, 1H), 8.62 (t, J=5.8 Hz, 1H), 7.79-7.70 (m, 2H), 7.60 (d, J=7.2 Hz, 1H), 5.09-5.02 (dd, J=5.3 and 12.5 Hz, 1H), 4.65 (d, J=5.8 Hz, 2H), 2.83-2.73 (m, 1H), 2.54-2.41 (m, 2H), 1.99-1.94 (m, 1H), 1.57 (m, 1H), 0.62-0.60 (m, 4H); ¹³C NMR (DMSO-*d*₆) δ 173.21, 172.85, 169.90, 167.52, 167.01, 139.44, 134.85, 133.37, 131.57, 127.13, 121.94, 48.89, 37.82, 30.97, 22.03, 13.58, 6.52; Anal. Calcd. For C₁₈H₁₇N₃O₅: C, 60.84; H, 4.82; N, 11.82. Found: C, 60.46; H, 4.84; N, 11.65.

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Methyl-3-[(Ethoxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate

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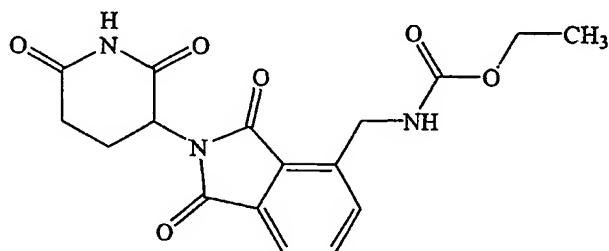
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Triethylamine (1.57 g, 18.5 mmol) was added to a stirred suspension of methyl-3-(aminomethyl)-2-(methoxycarbonyl)benzoate hydrochloride (2.0 g, 8 mmol) in dichloromethane (30 ml). The mixture was cooled in an ice bath to 4 °C. Ethyl chloroformate (1.0 g, 9 mmol) was added slowly keeping the mixture at 4-6 °C. After 5 addition was complete, the mixture was stirred in an ice bath for 30 minutes and then warmed to room temperature for 2 hours. The mixture was washed with water (2 × 30 ml), brine (30 ml) and dried. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (dichloromethane/ethyl acetate 95 to 5) to give 1.59 g (70%) of the product as an oil: ¹H NMR (CDCl₃) δ 7.87 (d, J=7.8 Hz, 1H), 7.36 (d, J=7.6 Hz, 1H), 7.46 10 (t, J=7.7 Hz, 1H), 5.30 (b, 1H), 4.32 (d, J=6.3 Hz, 2H), 4.12 (q, J=7.0 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 1.22 (t, J=7.2 Hz, 3H).

[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-carbamic acid ethyl ester I-5

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20



1,8-Diazabicyclo[5.4.0]undec-7-ene (0.8 g, 5 mmol) was added to a stirred suspension of methyl-3-[(ethoxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate 25 (1.54 g, 5 mmol) and aminoglutamide hydrochloride (0.86 g, 5 mmol) in DMF (15 ml). The mixture was heated to 120 °C for 24 hours. The mixture was cooled to room temperature and poured into water (150 ml). The mixture was extracted with ethyl acetate (3 × 30 ml) and the ethyl acetate solution was washed with water (30 ml), brine (30 ml) and dried. Solvent was removed and the residue was purified by flash chromatography 30 (dichloromethane/ethyl acetate 7 to 3) to give 0.84 g (45%) of the product as a white solid : mp 187-189 °C; ¹H NMR (DMSO-*d*₆) δ 11.03 (s, 1H), 7.76-7.58 (m, 4H), 5.06-4.99 (dd, J=5.4 and 12.6 Hz, 1H), 4.52 (d, J=5.9 Hz, 2H), 3.91 (q, J=7.0 Hz, 2H), 2.79-2.70 (m, 1H), 2.51-2.38 (m, 2H), 1.96-1.86 (m, 1H), 1.06 (t, J=7.0 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.89, 169.93, 167.55, 167.05, 156.72, 139.69, 134.91, 132.90, 131.58, 127.04, 121.97,

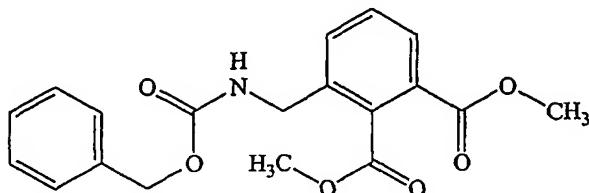
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60.15, 48.90, 39.34, 30.98, 22.04, 14.69; Anal. Calcd. For C₁₇H₁₇N₃O₆: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.94; H, 4.81; N, 11.37.

Methyl-3-[(benzyloxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate

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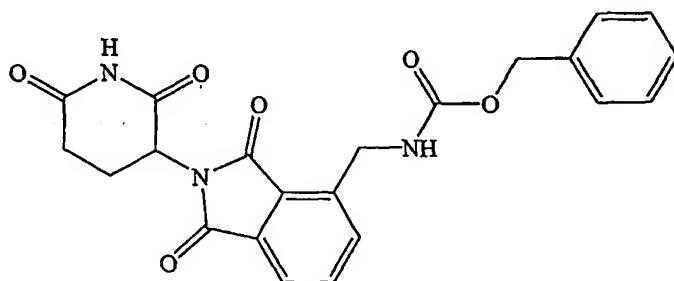


Triethylamine (1.87 g, 18.5 mmol) was added to a stirred suspension of methyl-3-(aminomethyl)-2-(methoxycarbonyl)benzoate hydrochloride (2.0 g, 8 mmol) in dichloromethane (30 ml). The mixture was cooled in an ice bath to 4 °C. Benzyl 15 chloroformate (1.66 g, 10 mmol) was added slowly keeping the temperature between 4-7 °C. After the addition was complete, the cooled mixture was stirred an additional 30 minutes and then warmed to room temperature for 4 hours. The mixture was washed with water (2 × 30 ml), brine (30 ml) and dried. Solvent was removed and the residue was purified by chromatography (dichloromethane/ethyl acetate 95 to 5) to give 2.1 g (76%) of 20 the product as a solid; ¹H NMR (CDCl₃) δ 7.87 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.6 Hz, 1H), 7.46 (t, J=7.7 Hz, 1H), 7.36-7.26 (m, 5H), 5.41 (b, 1H), 5.09 (s, 2H), 4.36 (d, J=6.3 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H).

[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl]-carbamic acid benzyl ester I-6

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1,8-diazabicyclo[5.4.0]undec-7-ene (0.88 g, 6 mmol) was added to a stirred suspension of methyl-3-[(benzyloxycarbonylamino)methyl]-2-(methoxycarbonyl)benzoate (2.07 g, 6 mmol) and aminoglutaramide hydrochloride (0.95 g, 6 mmol) in DMF (15 ml). The mixture was heated to 120 °C for 24 hours. The mixture was cooled to room

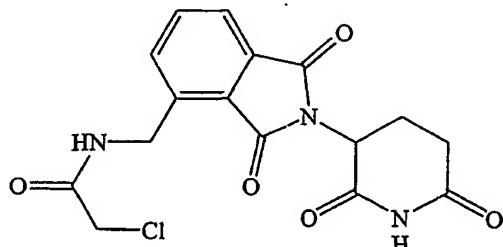
5 temperature and poured into water (150 ml). The mixture was extracted with ethyl acetate (3 × 30 ml) and the combined ethyl acetate extracts were washed with water (2 × 30 ml), brine (30 ml) and dried. Solvent was removed *in vacuo* and the residue was purified by chromatography (dichloromethane/ethyl acetate 8 to 2) to give 0.58 g (24%) of the product as a white solid: mp 166-168 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 7.99-7.71 (m, 4H),

10 7.37 (m, 5H), 5.19-5.12 (dd, J=5.1 and 17.4 Hz, 1H), 5.07 (s, 2H), 4.70 (d, J=5.7 Hz, 2H), 2.97-2.83 (m, 1H), 2.64-2.51 (m, 2H), 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.85, 169.89, 167.51, 167.01, 156.55, 139.46, 137.02, 134.87, 132.89, 131.57, 128.44, 127.92, 127.83, 127.06, 121.99, 65.69, 48.89, 30.97, 22.02; Anal. Calcd. For C₂₂H₁₉N₃O₆: C, 62.70; H, 4.54; N, 9.97. Found: C, 62.53; H, 4.57; N, 9.89.

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2-Chloro-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}acetamide I-7

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Triethylamine (0.6 g, 6 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.8 g, 2.5 mmol) in THF (70 ml). After stirring for 5 min, chloroacetyl chloride (0.34 g, 3 mmol) was added and the resulting mixture was heated at reflux for 3 hours. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (70 ml), washed with water (20 ml), 2N HCl (30 ml), water (2 × 30 ml), brine (30 ml) and dried. Solvent was removed *in vacuo* and the resulting solid was slurried in dichloromethane (10 ml) and ether (10 ml) and filtered to give 0.76 g (84%) of the product: ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 8.87 (t, J=5.9 Hz, 1H), 7.88-7.68 (m, 3H), 5.19-5.12 (dd, J=5.3 and 12.6 Hz, 1H), 4.77 (d, J=5.9 Hz, 2H), 4.19 (s, 2H), 2.96-2.83 (m, 1H), 2.65-2.51 (m, 2H), 2.11-2.04 (m, 1H); ¹³C NMR

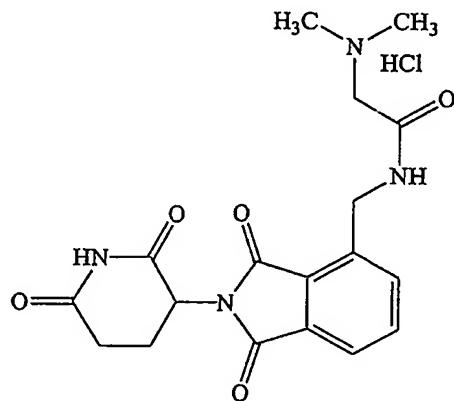
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(DMSO-*d*₆) δ 172.88, 169.90, 167.53, 167.01, 166.67, 138.46, 134.90, 133.22, 131.63, 127.26, 122.14, 48.94, 42.61, 38.27, 30.99, 22.05.

5 2-(Dimethylamino)-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-acetamide I-8, hydrochloride}

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Dimethylamine (2M in THF, 5 ml, 10 mmol) was added to a stirred suspension of 2-chloro-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}acetamide (1.2 g, 3.3 mmol) in acetonitrile (120 ml). The mixture was stirred at room temperature overnight.

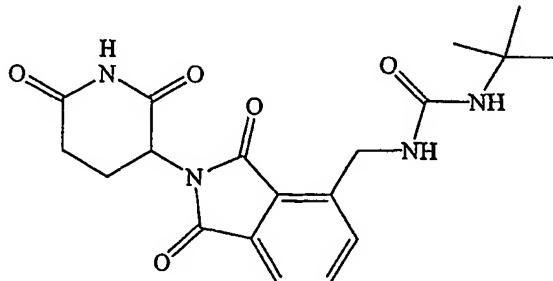
- 20 Solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (75 ml), washed with water (30 ml), brine (30 ml) and dried. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (dichloromethane/methanol 95 to 5) to give 0.96 g (78%) of the free base. The free base was dissolved in ethyl acetate (20 ml) and treated with 1N HCl (5 ml) to afford 0.9 g (86%) of the hydrochloride salt: mp 185-187 °C;
- 25 ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 10.05 (b, 1H), 9.40 (s, 1H), 7.84 (m, 3H), 5.14 (m, 1H), 4.81 (s, 2H), 4.07 (s, 2H), 2.84 (s, 6H), 2.65-2.52 (m, 3H), 2.09 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.81, 169.82, 167.40, 166.89, 164.77, 137.91, 134.88, 133.53, 131.55, 127.25, 122.23, 57.21, 48.88, 43.20, 37.91, 30.93, 21.89; Anal. Calcd. For C₁₈H₂₁N₄O₅Cl + 0.65 water : C, 51.41; H, 5.34; N, 13.32; Cl, 8.43. Found: C, 51.12; H, 5.20; N, 12.67; Cl, 8.45.

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1-*tert*-Butyl-3-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl]-urea I-9

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- 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.28 g, 1.9 mmol) was added to stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.9 mmol) in acetonitrile (50 ml). After stirring for 1 hour, *t*-butylisocyanate (0.21 g, 2 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (70 ml) and washed with 0.1 N HCl (20 ml), water (20 ml), brine (20 ml) and dried. The solvent was removed *in vacuo* and the resulting solid was recrystallized from ethanol/isopropyl ether to give 0.36 g (51%) of the product: mp 186-188 °C; ¹H NMR (DMSO-*d*₆) δ 11.04 (s, 1H), 7.77-7.59 (m, 3H), 6.17 (t, J=6.2 Hz, 1H), 5.86 (s, 1H), 5.08-5.01 (dd, J=5.4 and 12.4 Hz, 1H), 4.49 (d, J=6.0 Hz, 2H), 2.82-2.73 (m, 1H), 2.54 -2.40 (m, 2H), 1.98-1.94 (m, 1H), 1.12 (s, 9H); ¹³C NMR (DMSO-*d*₆) δ 172.33, 169.39, 167.11, 166.59, 156.85, 140.72, 134.20, 132.99, 131.06, 126.54, 121.20, 48.69, 48.37, 37.89, 30.46, 28.88, 21.53; Anal. Calcd. For C₁₉H₂₂N₄O₅ + 0.2 water : C, 58.51; H, 5.79; N, 14.37. Found: C, 58.86; H, 6.15; N, 14.24.

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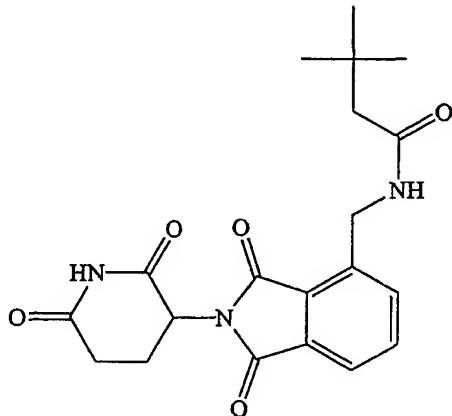
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-3,3-dimethylbutanamide I-10}

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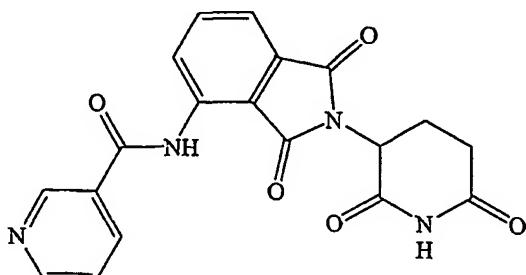
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15 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62 g, 4 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.9 mmol) in acetonitrile (50 ml). After stirring for 20 min, *t*-butylacetyl chloride (0.25 g, 1.9 mmol) was added. The mixture was stirred at room temperature for 17 hours. Solvent was removed *in vacuo* and the residue was dissolved in
20 dichloromethane (90 ml) and washed with 0.1N HCl (30 ml), water (30 ml), brine (30 ml) and then dried. Solvent was removed *in vacuo* and the solid residue was slurried in ethanol (10 ml) to give after filtration 0.55 g (77%) of the product: mp 145-147 °C; ¹H NMR (DMSO-*d*₆) δ 11.14 (s, 1H), 8.39 (t, J=5.7 Hz, 1H), 7.87-7.69 (m, 3H), 5.19-5.12 (dd, J=5.3 and 12.4 Hz, 1H), 4.72 (d, J=5.8 Hz, 2H), 2.92-2.83 (m, 1H), 2.63-2.51 (m, 2H), 2.08 (s, 2H), 2.08-2.04 (m, 1H), 0.97 (s, 9H); ¹³C NMR (DMSO-*d*₆) δ 172.69, 171.35, 169.74, 167.51, 166.96, 139.61, 134.69, 133.41, 131.52, 127.11, 121.87, 48.86, 48.62, 37.53, 30.93, 30.52, 29.71, 22.00; Anal. Calcd. For C₂₀H₂₃N₃O₅ + 0.28 water : C, 61.52; H, 6.08; N, 10.76. Found: C, 61.23; H, 6.18; N, 10.57.

N-[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]-3-pyridylcarboxamide I-11

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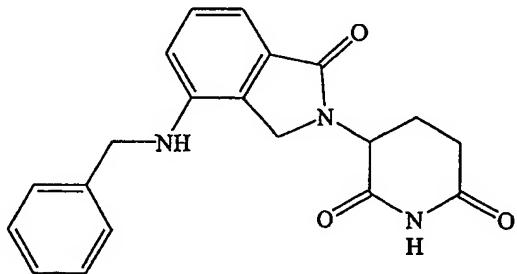


A stirred mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.09 g, 4.0 mmol) and nicotinoyl chloride hydrochloride (1.42 g, 8.0 mmol) in tetrahydrofuran (60 ml) was heated to reflux for 22 h. The suspension was filtered and washed with 5 tetrahydrofuran (20 ml) and ether (10 ml) to yield a white solid. The solid was slurried in pH 7 buffer (40 ml) and ether (30 ml) for 1h. The suspension was filtered and washed with water (20 ml) and ether (20 ml) to N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]-3-pyridylcarboxamide as a white solid (1.2 g, 79% yield): mp, 176-178 °C; ¹H NMR (DMSO-*d*₆) δ 2.06-2.10 (m, 1H, CHH), 2.49-2.65 (m, 2H, CH₂), 2.83-2.97 (m, 1H, CHH), 10 5.18 (dd, *J* = 5.3, 12.5 Hz, 1H, NCH), 7.64 (dd, *J* = 4.9, 7.9 Hz, 1H, Ar), 7.71 (d, *J* = 7.3 Hz, 1H, Ar), 7.92 (t, *J* = 7.8 Hz, 1H, Ar), 8.29-8.34 (m, 1H, Ar), 8.45 (d, *J* = 8.2 Hz, 1H, Ar), 8.83 (dd, *J* = 1.2, 4.8 Hz, 1H, Ar), 9.15 (d, *J* = 1.7 Hz, 1H, Ar), 10.55 (s, 1H, NH), 11.17 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 21.99, 30.93, 49.00, 119.06, 119.34, 123.91, 127.36, 129.17, 131.55, 135.24, 135.94, 136.20, 148.47, 152.95, 163.85, 166.59, 167.54, 15 169.69, 172.72; Anal Calcd for C₁₉H₁₄N₄O₅ + 0.13 H₂O: C, 59.95; H, 3.78; N, 14.72; H₂O, 0.62. Found: C, 59.83; H, 3.66; N, 14.68; H₂O, 0.64.

3-{1-Oxo-4-[benzylamino]isoindolin-2-yl}piperidine-2,6-dione I-12

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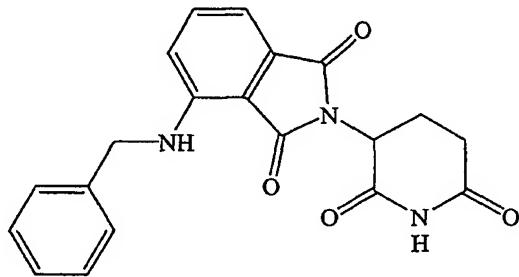
A stirred mixture of 3-(4-amino-1-oxoisooindolin-2-yl)piperidine-2,6-dione (518 mg, 2.0 mmol) and benzaldehyde (0.21 ml, 2.0 mmol) in methanol (20 ml) was heated to reflux for 5 h. The solvent was removed *in vacuo* to give a solid. The solid was re-dissolved in 30 acetic acid (20 ml). The stirred solution was heated to reflux for 1h, and was then allowed to cool to room temperature. To the stirred solution was added sodium borohydride (90 mg, 2.3 mmol) and stirring continued at room temperature for 18h. The resulting suspension was filtered and washed with acetic acid (10 ml) and ether (20 ml) to give 3-{1-oxo-4-[benzylamino]isoindolin-2-yl}piperidine-2,6-dione as an off-white solid (420 mg, 35 60% yield): mp, 257-259 °C; ¹H NMR (DMSO-*d*₆) δ 2.01-2.07 (m, 1H, CHH), 2.23-2.30

(m, 1H, CHH), 2.49-2.65 (m, 1H, CHH), 2.85-3.00 (m, 1H, CHH), 4.19 (d, $J = 17$ Hz, 1H, CHH), 4.31 (d, $J = 17$ Hz, 1H, CHH), 4.39 (d, $J = 5.7$ Hz, 2H, CH₂), 5.12 (dd, $J = 5.1, 13$ Hz, 1H, NCH), 6.37 (t, $J = 5.9$ Hz, 1H, NH), 6.62 (d, $J = 8.0$ Hz, 1H, Ar), 6.91 (d, $J = 7.3$ Hz, 1H, Ar), 7.19-7.40 (m, 6H, Ar), 11.02 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 22.79, 5 31.25, 45.79, 46.09, 51.56, 110.32, 112.34, 126.72, 127.05, 128.32, 129.07, 132.08, 139.72, 143.33, 168.82, 171.22, 172.90; Anal Calcd for C₂₀H₁₉N₃O₃: C, 68.75; H, 5.48; N, 12.03. Found C, 68.73; H, 5.41; N, 12.04.

2-(2,6-Dioxo(3-piperidyl))-4-[benzylamino]isoindoline-1,3-dione I-13

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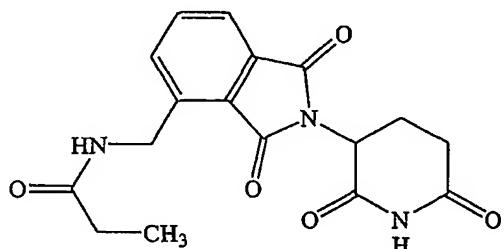
A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.0 g, 3.7 mmol) and benzaldehyde (0.4 ml, 3.9 mmol) in acetic acid (20 ml) was stirred at room temperature for 17h, then was heated to reflux for 3h. The mixture was cooled to room 20 temperature. To the stirred mixture was added sodium borohydride (140 mg, 3.7 mmol) and kept at room temperature for 18h. The mixture was then heated to reflux for 2h. To the mixture was added additional benzaldehyde (0.4 ml, 3.9 mmol) during reflux. After 30 min of reflux the reaction was allowed to cool to room temperature. To the mixture was added sodium borohydride (180 mg, 4.8 mmol) and the mixture stirred at room temperature 25 for 3 days. The solvent was removed *in vacuo* to yield an oil. The oil was diluted with ethyl acetate (90 ml) and aqueous sodium hydrogen carbonate (sat, 100 ml). The organic layer was separated and was washed with aqueous sodium hydrogen carbonate (sat, 2 × 100 ml), brine (100 ml) and dried over MgSO₄. The solvent was removed *in vacuo* to give a solid. The solid was purified by column chromatography (Silica Gel, 50% EtOAc:CH₂Cl₂) 30 to give a yellow solid. The solid was further purified by column chromatography (KP-C18-HS, 35:65 CH₃CN:0.1% CF₃COOH in water) to give 2-(2,6-dioxo(3-piperidyl))-4-[benzylamino]isoindoline-1,3-dione as a yellow solid (210 mg, 16% yield): mp, 209-211 °C; ¹H NMR (DMSO-d₆) δ 2.02-2.08 (m, 1H, CHH), 2.46-2.63 (m, 2H, CH₂), 2.82-2.97 (m, 1H, CHH), 4.56 (d, $J = 6.2$ Hz, 2H, CH₂), 5.07 (dd, $J = 5.3, 12.4$ Hz, 1H, NCH), 6.96 (d, $J = 8.6$ Hz, 1H, Ar), 7.02 (d, $J = 7.0$ Hz, 1H, Ar), 7.19-7.40 (m, 6H, Ar, NH), 7.51 (dd, J

= 7.5, 8.4 Hz, 1H, Ar), 11.11 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆) δ 22.15, 30.99, 45.44, 48.59, 109.58, 110.74, 117.63, 126.95, 126.99, 128.53, 132.21, 136.09, 138.95, 146.09, 167.27, 168.78, 170.07, 172.79; Anal Calcd for C₂₀H₁₇N₃O₄: C, 66.11; H, 4.72; N, 11.56. Found: C, 65.96; H, 4.60; N, 11.49.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide I-14}

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.65 g, 4.25 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, propionyl chloride (0.2 g, 2.13 mmol) was added. The mixture was stirred at room temperature for 17 hours. Solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (60 ml) and washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed and the resulting solid was slurried in hot C₂H₅OH (10 ml) to give after filtration N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide (0.41 g, 64%) as a white solid: mp 219-221°C; ¹H NMR (DMSO-*d*₆) δ d 11.15 (s, 1H), 8.42 (t, J=5.8 Hz, 1H), 7.87-7.67 (m, 3H), 5.19-5.12 (dd, J=5.3 and 12.5 Hz, 1H), 4.72 (d, J=5.8 Hz, 2H), 2.98-2.84 (m, 1H), 2.65-2.48 (m, 2H), 2.26-2.17 (m, 2H), 2.09-2.04 (m, 1H), 1.05 (t, J=7.8 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ d 173.52, 172.81, 169.79, 167.53, 167.01, 139.52, 134.79, 133.20, 131.55, 127.10, 121.86, 48.89, 37.69, 30.95, 28.43, 22.03, 9.90; Anal. Calcd. For C₁₇H₁₇N₃O₅ + 0.19 H₂O: C, 58.88; H, 5.05; N, 12.12. Found: C, 58.77; H, 30 4.97; N, 12.12.

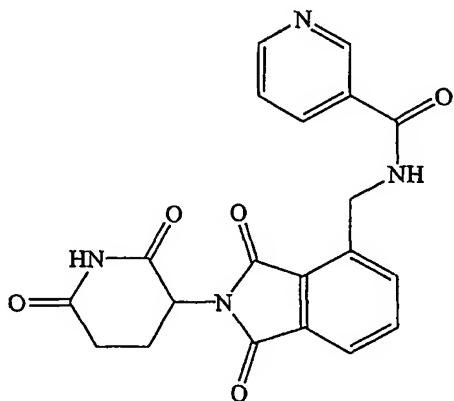
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-3-pyridylcarboxamide I-

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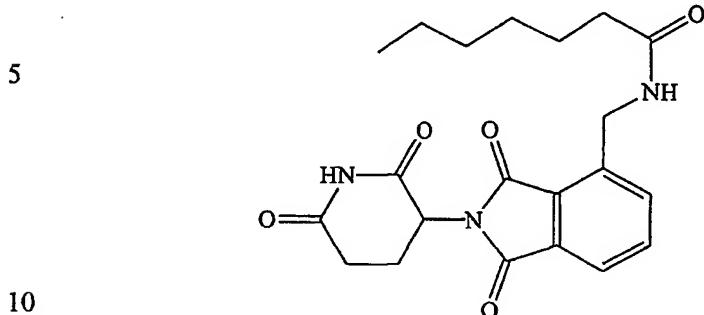
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15 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.98 g, 6.48 mmol) was added to stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, nicotinoyl chloride (0.41 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂, CH₂Cl₂: CH₃OH 97.5:2.5) to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-3-pyridylcarboxamide (0.47 g, 64%) as a white solid: mp 148-151°C; ¹H NMR (DMSO-*d*₆) δ d 11.16 (s, 1H), 9.36 (t, J=5.6 Hz, 1H), 9.09 (d, J=1.25 Hz, 1H), 8.75-8.73 (m, 1H), 8.25 (d, J=8.0 Hz, 1H), 7.84-7.76 (m, 3H), 7.57-7.52 (m, 1H), 5.22-5.15 (dd, J=5.4 and 12.7 Hz, 1H), 4.96 (d, J=5.6 Hz, 2H), 2.92-2.85 (m, 1H), 2.65-2.50 (m, 2H), 2.11-2.06 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ d 172.72, 169.80, 167.51, 166.94, 165.23, 152.02, 148.44, 138.86, 135.10, 134.83, 133.20, 131.55, 129.48, 127.20, 123.49, 121.95, 48.89, 38.33, 30.93, 21.98; Anal. Calcd. For C₂₀H₁₆N₄O₅ + 0.28 H₂O: C, 60.45; H, 4.20; N, 14.10. Found: C, 60.29; H, 4.28; N, 13.82.

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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}heptanamide I-16

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.65 g, 2.22 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, heptanoyl 15 chloride (0.33 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 7: 3) to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3- 20 dioxoisooindolin-4-yl]methyl}heptanamide (0.49 g, 66%) as a white solid: mp 130-132°C; ¹H NMR (DMSO-*d*₆) δ d 11.14 (s, 1H), 8.44 (t, J=5.7 Hz, 1H), 7.86-7.78 (m, 2H), 7.71- 7.65 (m, 1H), 5.19-5.12 (dd, J=5.2 and 12.4 Hz, 1H), 4.69 (d, J=5.7 Hz, 2H), 2.98-2.83 (m, 1H), 2.64-2.50 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.08-2.04 (m, 1H), 1.53 (t, J=6.0 Hz, 2H), 1.25 (s, 6H), 0.85 (t, J=5.9 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ d 172.73, 172.66, 169.79, 25 167.47, 166.93, 139.54, 134.66, 133.13, 131.50, 127.06, 121.80, 54.86, 48.85, 37.57, 35.23, 30.96, 28.31, 25.16, 21.97, 13.87; Anal. Calcd. For C₂₁H₂₅N₃O₅ + 0.3 H₂O: C, 62.30; H, 6.37; N, 10.38. Found : C, 62.07; H, 6.29; N, 10.23.

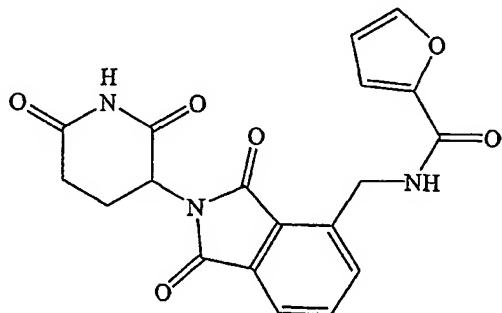
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-furylcarboxamide I-17

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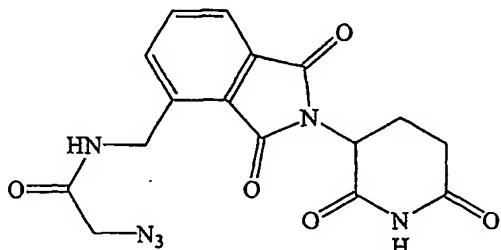
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.650 g, 2.22 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.600 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, 2-furoyl chloride (0.290 g, 2.22 mmol) was added and the mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1: 1) to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-furylcarboxamide (0.51 g, 73%) as a white solid: mp 121-123°C; ¹H NMR (DMSO-*d*₆) δ d 11.13 (s, 1H), 9.01 (t, J=5.7 Hz, 1H), 7.88-7.68 (m, 4H), 7.18 (d, J=3.3 Hz, 1H), 6.66 (m, 1H), 5.20-5.13 (dd, J=5.4 and 12.5 Hz, 1H), 4.90 (d, J=5.6 Hz, 2H), 2.97-2.84 (m, 1H), 2.65-2.49 (m, 2H), 2.10-1.98 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ d 172.73, 169.80, 167.52, 166.94, 158.09, 147.49, 145.27, 139.06, 134.80, 132.98, 131.52, 127.09, 121.88, 113.86, 111.91, 48.86, 37.64, 30.92, 21.97; Anal. Calcd. For C₁₉H₁₅N₃O₆ + 0.18 H₂O: C, 59.34; H, 4.03; N, 10.93. Found: C, 59.47; H, 4.16; N, 10.49.

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2-Azido-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-acetamide I-18

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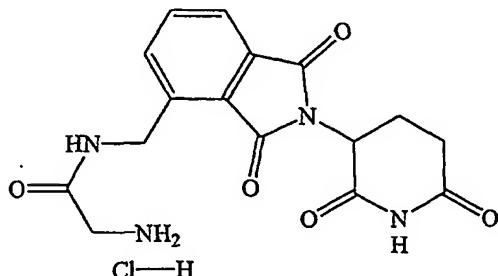
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A mixture of 2-chloro-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}acetamide (1.3 g, 3.57 mmol), sodium azide (0.3 g, 4.65 mmol) and sodium iodide (0.54 g, 3.57 mmol) in acetone (50 ml) was refluxed for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (60 ml). The EtOAc solution was washed with H₂O (30 ml), brine (30 ml), and dried (MgSO₄). The solvent was removed *in vacuo* to give 2-azido-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}acetamide (1.2 g, 90%) as a white solid: ¹H NMR (CDCl₃) δ d 8.48 (s, 1H), 7.84-7.68 (m, 3H), 7.51 (t, J=6.3 Hz, 1H), 5.04-4.97 (dd, J=4.7 and 11.8 Hz, 1H), 4.80 (d, J=6.5 Hz, 2H), 3.97 (s, 2H), 2.95-2.74 (m, 3H), 2.20-2.15 (m, 1H).

2-Amino-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}acetamide I-19 hydrochloride

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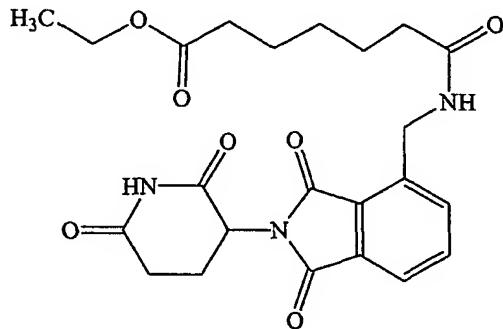
A mixture of 2-azido-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}acetamide (1.2 g, 3.24 mmol), and 10% Pd/C (0.15 g) in 4N HCl (20 ml) and CH₃OH (50 ml) was hydrogenated in Parr shake apparatus under 50 psi of hydrogen for 3

hours. The mixture was then filtered through celite and the filtrate was concentrated to a solid residue. The solid was slurried in ethanol (20 ml) and the suspension filtered to give 2-amino-N-{{[2-(2,6-dioxo(3-piperidyl))1,3-dioxoisooindolin-4-yl]methyl}acetamide hydrochloride (0.86 g, 84%) as a white solid: mp 270-272°C; ¹H NMR (DMSO-*d*₆) δ d 11.16 (s, 1H), 9.28 (t, J=5.7 Hz, 1H), 8.33 (s, 3H), 7.83 (s, 3H), 5.20-5.13 (dd, J=5.3 and 12.5 Hz, 1H), 4.81 (d, J=5.7 Hz, 2H), 3.69 (s, 2H), 2.92-2.87 (m, 1H), 2.65-2.51 (m, 2H), 2.09-2.05 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ d 172.76, 169.80, 167.44, 166.91, 166.52, 138.24, 134.74, 133.53, 131.51, 127.17, 122.08, 48.89, 37.89, 30.94, 21.99; Anal. Calcd. For C₁₆H₁₇N₄O₅Cl: C, 50.47; H, 4.50; N, 14.71; Cl, 9.31. Found: C, 50.39; H, 4.61; N, 14.42; Cl, 9.25.

Ethyl 6-(N-{{[2-(2,6-dioxo(3-piperidyl))1,3-dioxoisooindolin-4-yl]methyl}carbamoyl})hexanoate I-20

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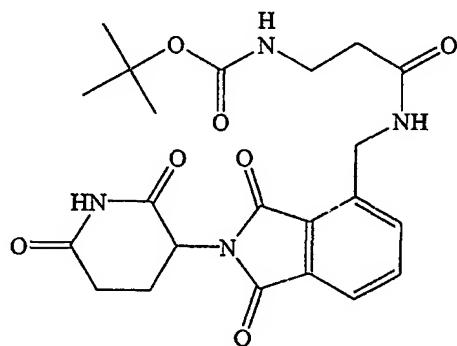
25 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.65 g, 4.26 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, 6-(chloroformyl)hexanoic acid ethyl ester (0.46 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1:1) to give ethyl 6-(N-{{[2-(2,6-dioxo(3-piperidyl))1,3-dioxoisooindolin-4-yl]methyl}carbamoyl})hexanoate (0.43 g, 50%) as a white solid: mp 82-84°C; ¹H NMR (DMSO-*d*₆) δ d 11.11 (s, 1H), 8.41 (t, J=5.6 Hz, 1H), 7.86-7.65 (m, 3H), 5.18-5.11 (dd, J=5.4 and 12.4 Hz, 1H), 4.72 (d, J=5.7

Hz, 2H), 4.05 (q, J=7.1 Hz, 2H), 2.97-2.83 (m, 1H), 2.64-2.48 (m, 2H), 2.30-2.15 (m, 4H), 2.08-2.04 (m, 1H), 1.56-1.47 (m, 4H), 1.32-1.23 (m, 2H), 1.17 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ d 172.80, 172.71, 172.52, 169.77, 167.45, 166.92, 139.49, 134.67, 133.13, 131.49, 127.04, 121.78, 59.60, 48.84, 37.57, 35.02, 33.38, 30.91, 28.08, 24.83, 24.16, 5 21.96, 14.09; Anal. Calcd. For $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_7$: C, 60.39; H, 5.95; N, 9.18. Found: C, 60.10; H, 5.82; N, 8.82.

3-[*(tert*-Butoxy)carbonylamino]-*N*-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide I-21

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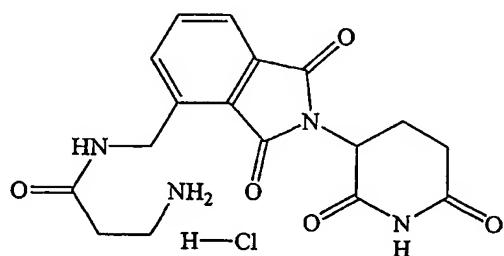
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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.7 g, 4.62 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH_3CN (50 ml). After stirring for 20 min, 1-hydroxybenzotriazole (0.3 g, 2.22 mmol), N-BOC-b-alanine (0.42 g, 2.22 mol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride 0.53 g, 2.78 mmol) were added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (70 ml). The CH_2Cl_2 solution was washed with 1N citric acid (30 ml), H_2O ($2 \times$ 30 ml), brine (30 ml) and dried (MgSO_4). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO_2 , 25 CH_2Cl_2 ; CH_3OH 100:2) to give 3-[*(tert*-butoxy)carbonylamino]-*N*-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide (0.57 g, 67%) as a white solid: mp 96-98°C; ^1H NMR (DMSO- d_6) δ d 11.14 (s, 1H), 8.50 (t, J=5.8 Hz, 1H), 7.82-7.67 (m, 3H), 6.81 (t, J=5.1 Hz, 1H), 5.19-5.11 (dd, J=5.4 and 12.4 Hz, 1H), 4.72 (d, J=5.7 Hz, 2H), 3.21-3.13 (dd, J=6.8 and 13.1 Hz, 2H), 2.92-2.85 (m, 1H), 2.64-2.33 (m, 4H), 2.08-2.04 (m, 30 1H), 1.37 (s, 9H); ^{13}C NMR (DMSO- d_6) δ d 172.71, 170.87, 169.77, 167.46, 166.93, 35 1H).

155.45, 139.27, 134.67, 133.17, 131.47, 127.03, 121.80, 77.57, 48.84, 37.63, 36.69, 35.62,
 30.91, 28.21, 21.96; Anal. Calcd. For $C_{22}H_{26}N_4O_7 + 0.28 H_2O$: C, 57.01; H, 5.78; N, 12.09.
 Found: C, 56.99; H, 5.89; N, 11.79.

5 3-Amino-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide I-22, hydrochloride

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A 4N HCl solution in dioxane (1 ml) was added to a stirred solution of 3-[*(tert*-butoxy)carbonylamino]-*N*-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide (0.5 g, 1.09 mmol) in CH_2Cl_2 (15 ml) and stirred for 17 hours. The resulting suspension was filtered to give 3-amino-*N*-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}propanamide hydrochloride (0.34 g, 79%) as a white solid:
 mp 161-163°C; 1H NMR ($DMSO-d_6$) δ d 11.15 (s, 1H), 8.88 (t, $J=5.8$ Hz, 1H), 8.06 (b, 3H), 7.87-7.79 (m, 3H), 5.19-5.12 (dd, $J=5.3$ and 12.6 Hz, 1H), 4.76 (d, $J=5.8$ Hz, 2H), 3.03-2.84 (m, 3H), 2.67-2.47 (m, 4H), 2.08-2.04 (m, 1H); ^{13}C NMR ($DMSO-d_6$) δ d 172.74, 169.88, 169.80, 167.45, 166.92, 138.92, 134.74, 133.46, 131.48, 127.09, 121.92, 48.86, 37.69, 35.11, 32.03, 30.92, 21.97; Anal. Calcd. For $C_{17}H_{19}N_4O_5Cl + 0.13 CH_2Cl_2 + 0.57 H_2O$: C, 49.44; H, 4.94; N, 13.46; Cl, 10.73. Found: C, 49.22; H, 4.88; N, 13.08; Cl, 10.95.

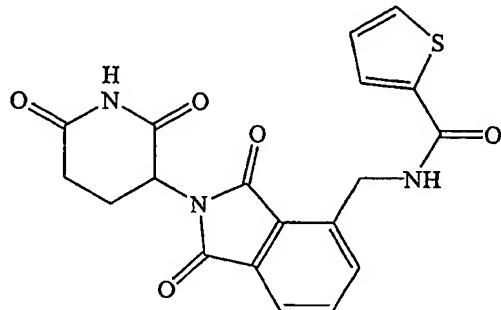
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2-thienylcarboxamide I-
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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.620 g; 4.07 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione hydrochloride (0.600 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, 2-thiophene-carbonyl chloride (0.3 g, 2.03 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 6:4) to give N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl]-2-thienylcarboxamide (0.35 g, 47%) as a white solid: mp 192-194°C; ¹H NMR (DMSO-*d*₆) δ d 11.16 (s, 1H), 9.18 (t, J=5.8 Hz, 1H), 7.88-7.72 (m 5H), 7.20-7.17 (dd, J=3.9 and 4.7 Hz, 1H), 5.22-5.15 (dd, J=5.5 and 12.7 Hz, 1H), 4.94 (d, J=5.8 Hz, 2H), 2.98-2.85 (m, 1H), 2.66-2.50 (m, 2H), 2.11-2.06 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ d 172.72, 169.80, 167.51, 166.93, 161.52, 139.26, 139.14, 134.83, 133.14, 131.53, 131.11, 128.51, 127.96, 127.12, 121.93, 48.89, 38.09, 30.93, 21.99; Anal. Calcd. For C₁₉H₁₅N₃O₅S: C, 57.42; H, 3.80; N, 10.57; S, 8.07. Found: C, 57.80; H, 3.93; N, 10.22; S, 7.99.

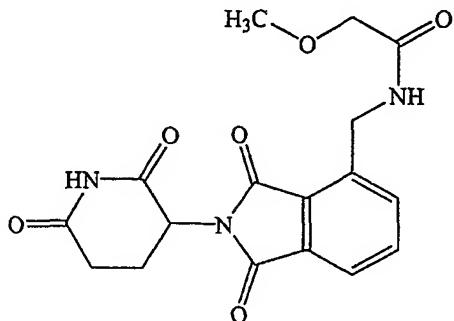
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-methoxyacetamide I-
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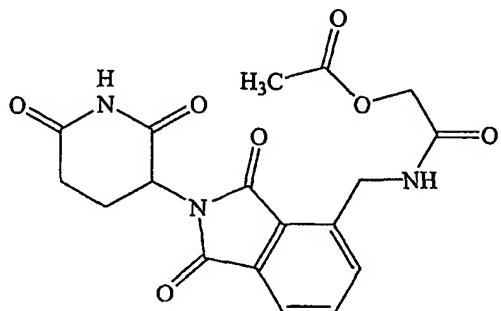
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62 g, 4.07 mmol) was added to a stirred
 15 suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione
 hydrochloride (0.600 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min,
 methoxyacetyl chloride (0.22 g, 2.03 mmol) was added. The mixture was stirred at room
 temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved
 in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml),
 20 brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was
 purified by chromatography (SiO₂, CH₂Cl₂; CH₃OH 100:2.5) to give N-{[2-(2,6-dioxo(3-
 piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-methoxyacetamide (0.44 g, 66%) as a white
 solid: mp 196-198°C; ¹H NMR (DMSO-*d*₆) δ d 11.14 (s, 1H), 8.49 (t, J=6.1 Hz, 1H), 7.86-
 7.79 (m, 2H), 7.68-7.65 (m, 1H), 5.19-5.12 (dd, J=5.3 and 12.5 Hz, 1H), 4.77 (d, J=6.1 Hz,
 2H), 3.92 (s, 2H), 3.36 (s, 3H), 2.96-2.83 (m, 1H), 2.64-2.49 (m, 2H), 2.09-2.04 (m, 1H);
 25 ¹³C NMR (DMSO-*d*₆) δ d 172.71, 169.78, 169.58, 167.52, 166.94, 139.09, 134.70, 133.00,
 131.51, 127.08, 121.82, 71.46, 58.70, 48.86, 37.47, 30.91, 21.95; Anal. Calcd. For
 C₁₇H₁₇N₃O₆: C, 56.82; H, 4.77; N, 11.69. Found: C, 57.02; H, 4.87; N, 11.36.

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(N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}carbamoyl)methyl acetate I-25}

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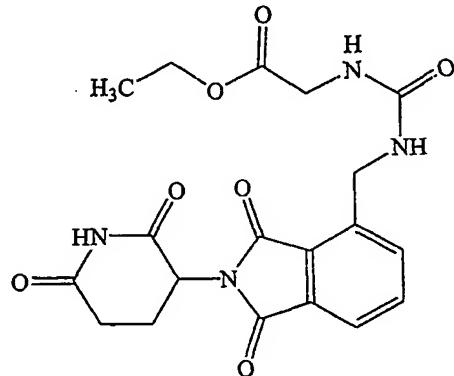
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62 g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.600 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, acetoxyacetyl chloride (0.28 g, 2.03 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃OH 100:2.5) to give (N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}carbamoyl)methyl acetate (0.54 g, 75%) as a white solid: mp 108-110°C; ¹H NMR (DMSO-*d*₆) δ d 11.14 (s, 1H), 8.68 (t, J=6.0 Hz, 1H), 7.87-7.79 (m, 2H), 7.71-7.65 (m, 1H), 5.19-5.12 (dd, J=5.3 and 12.4 Hz, 1H), 4.77 (d, J=5.9 Hz, 2H), 4.56 (s, 2H), 2.96-2.83 (m, 1H), 2.63-2.47 (m, 2H), 2.11 (s, 3H), 2.08-1.98 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ d 172.66, 169.96, 169.72, 167.46, 167.37, 166.36, 138.80, 134.68, 133.01, 132.47, 127.04, 121.87, 62.36, 48.84, 37.46, 30.38, 21.93, 20.49; Anal. Calcd. For C₁₈H₁₇N₃O₇ + 0.15H₂O: C, 55.43; H, 4.47; N, 10.77. Found: C, 55.43; H, 4.54; N, 10.44.

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Ethyl 2-[(N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}carbamoyl)amino]acetate I-26

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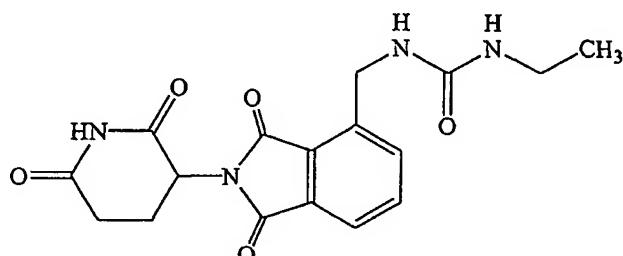
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29 g, 1.9 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, ethyl isocyanataacetate (0.29 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCl (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1:1) to give ethyl 2-[(N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}carbamoyl)amino]acetate (0.30 g, 39%) as a white solid: mp 187-189°C; ¹H NMR (DMSO-*d*₆) δ d 11.14 (s, 1H), 7.86-7.70 (m, 3H), 6.83 (t, J=6.1 Hz, 1H), 6.53 (t, J=6.0 Hz, 1H), 5.18-5.11 (dd, J=5.4 and 12.5 Hz, 1H), 4.65 (d, J=6.0 Hz, 2H), 4.09 (q, J=7.2 Hz, 2H), 3.79 (d, J=6.0 Hz, 2H), 2.98-2.83 (m, 1H), 2.64-2.48 (m, 2H), 2.08-2.04 (m, 1H), 1.18 (t, J=7.2 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ d 172.72; 171.01, 169.78, 167.54, 167.00, 158.00, 140.78, 134.57, 133.25, 131.48, 126.95, 121.66, 60.17, 48.83, 41.58, 38.72, 30.91, 21.97, 14.06; Anal. Calcd. For C₁₉H₂₀N₄O₇: C, 54.81; H, 4.84; N, 13.46. Found: C, 54.73; H, 4.77; N, 13.35.

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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(ethylamino)carboxamide
I-27

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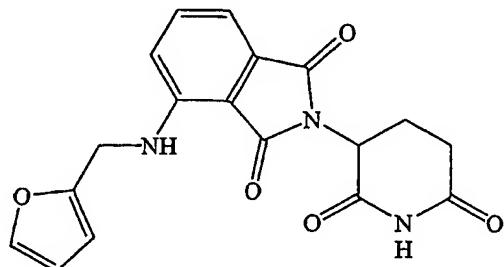
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29 g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60 g, 1.85 mmol) in CH₃CN (50 ml). After stirring for 20 min, ethyl 15 isocyanate (0.16 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 ml). The CH₂Cl₂ solution was washed with 1N HCL (30 ml), H₂O (30 ml), brine (30 ml) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃CN 6:4) to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3-20 dioxoisooindolin-4-yl]methyl}(ethylamino)carboxamide (0.2 g, 30%) as a white solid: mp 173-175 °C; ¹H NMR (DMSO-*d*₆) δ d 11.13 (s, 1H), 7.86-7.69 (m, 3H), 6.44 (t, J=6.1 Hz, 1H), 6.11 (t, J=5.55 Hz, 1H), 5.18-5.11 (dd, J=5.4 and 12.6 Hz, 1H), 4.63 (d, J=6.1 Hz, 2H), 3.07-2.83 (m, 3H), 2.64-2.49 (m, 2H), 2.08-2.04 (m, 1H), 0.99 (t, J=7.1 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ d 172.73, 169.80, 167.58, 167.03, 157.93, 141.15, 134.61, 133.37, 25 131.49, 126.96, 121.61, 48.83, 38.71, 34.17, 30.92, 21.98, 15.58; Anal. Calcd. For C₁₇H₁₈N₄O₅ + 0.14 H₂O: C, 56.58; H, 5.11; N, 15.53. Found: C, 56.56; H, 5.05; N, 15.28.

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2-(2,6-Dioxo(3-piperidyl))-4-[(2-furylmethyl)amino]isoindoline-1,3-dione I-28

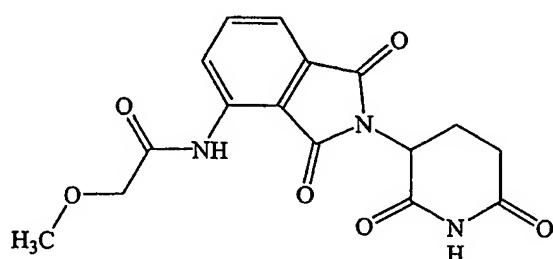
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10 To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in acetic acid (20 ml) was added furan-2-carbaldehyde (0.20 g, 2.05 mmol). The mixture was heated to reflux for 5 hours and allowed to cool at room temperature. Sodium borohydride (80 mg, 2 mmol) was added to the reaction mixture. The reaction mixture was stirred for 24 hours. The solvent was evaporated *in vacuo* and the residue was 15 dissolved in ethyl acetate (100 ml), washed with H₂O (3 × 100 ml), saturated aqueous NaHCO₃ (2 × 100 ml), brine (1 × 100 ml), and dried. The solvent was evaporated and the residue was purified by chromatography (ethyl acetate/hexane, 1:1) to give 0.25 g (35%) of product as a yellow solid: mp 171-173°C; ¹H NMR (DMSO-*d*₆) δ 11.10 (s, 1H), 7.58 (t, J=7.1 Hz, 2H), 7.18 (d, J=8.6 Hz, 1H), 7.08-6.97 (m, 2H), 6.39-6.36 (m, 2H), 5.06 (dd, J=5.2 and 12.4 Hz, 1H), 4.57 (d, J=6.0 Hz, 2H), 2.96-2.82 (m, 1H), 2.63-2.46 (m, 2H), 2.06-2.02 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.76, 170.01, 168.75, 167.21, 151.97, 145.81, 142.42, 136.05, 132.09, 117.60, 111.04, 110.42, 109.73, 107.38, 48.57, 30.95, 22.10; Anal. Calcd. For C₁₈H₁₅N₃O₅: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.02; H, 4.24; N, 11.81.

20 N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-methoxyacetamide I-29

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To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added 2-methoxyacetyl chloride (0.43 g, 4.0 mmol). The stirred mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.69 g (100 %)

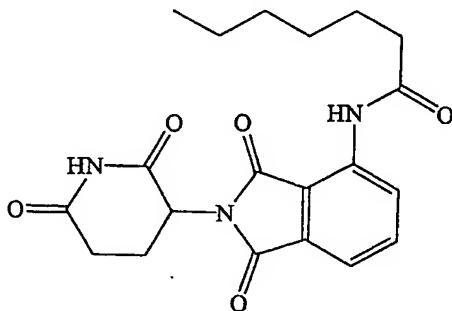
5 of product as an off-white solid: mp 246-248 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 10.30 (s, 1H), 8.70 (d, J=8.4 Hz, 1H), 7.86 (t, J=7.8 Hz, 1H), 7.63 (d, J=7.3 Hz, 1H), 5.17 (dd, J=5.2 and 12.7 Hz, 1H), 4.11 (s, 2H), 3.49 (s, 3H), 2.98-2.84 (m, 1H), 2.66-2.47 (m, 2H), 2.12-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.67, 169.66, 169.02, 168.25, 166.61, 136.48, 135.91, 131.24, 124.35, 118.31, 116.04, 71.40, 59.10, 48.96, 30.91, 21.94; Anal.

10 Calcd. For C₁₆H₁₅N₃O₆ : C, 55.65; H, 4.38; N, 12.17. Found: C, 55.58; H, 4.40; N, 12.08.

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]heptanamide I-30

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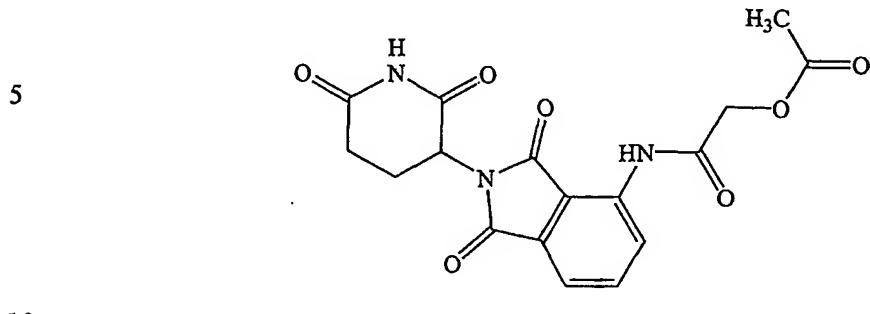


To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added heptanoyl chloride (0.59 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.61 g (79 %) of

25 product as an off-white solid: mp 200-202 °C; ¹H NMR (DMSO-*d*₆) δ 11.16 (s, 1H), 9.65 (s, 1H), 8.48 (d, J=8.3 Hz, 1H), 7.81 (t, J=7.7 Hz, 1H), 7.58 (d, J=7.2 Hz, 1H), 5.15 (dd, J=4.8 and 12.2Hz, 1H), 2.97-2.87 (m, 1H), 2.65-2.43 (m, 4H), 2.10-2.06 (m, 1H), 1.61-1.58 (m, 2H), 1.28 (bs, 6H), 0.85 (bs, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.67, 171.96, 169.69, 167.78, 166.61, 136.62, 136.04, 131.36, 125.97, 118.13, 116.67, 48.93, 36.56, 30.95, 28.16,

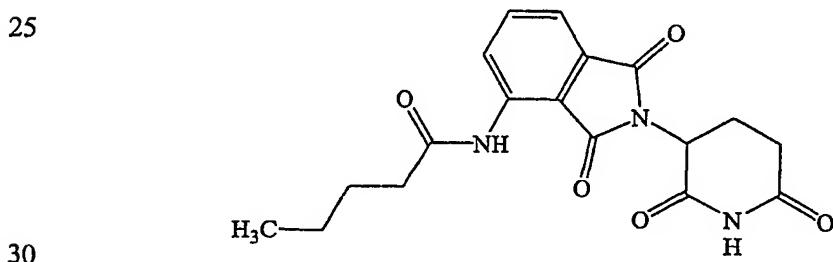
30 24.69, 21.94, 13.84; Anal. Calcd. For C₂₀H₂₃N₃O₅ : C, 62.33; H, 6.02; N, 10.90. Found: C, 62.14; H, 6.05; N, 10.72.

{N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]carbamoyl}methyl acetate I-31



To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added (chlorocarbonyl)methyl acetate (0.55 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.56 g
 15 (75 %) of product as an off-white solid: mp 234-236 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 10.06 (s, 1H), 8.55 (d, J=8.3 Hz, 1H), 7.87 (t, J=8.0 Hz, 1H), 7.65 (d, J=7.2 Hz, 1H), 5.17 (dd, J=5.0 and 12.4 Hz, 1H), 4.78 (s, 2H), 2.99-2.85 (m, 1H), 2.65-2.52 (m, 2H), 2.22 (s, 2H), 2.11-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.70, 169.69, 169.50, 167.99, 166.57, 136.40, 135.59, 131.35, 125.34, 118.72, 116.96, 62.60, 48.98, 30.90, 21.91, 20.41; Anal.
 20 Calcd. For C₁₇H₁₅N₃O₇ : C, 54.69; H, 4.05; N, 11.26. Found: C, 54.43; H, 4.05; N, 10.97.

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]pentanamide I-32



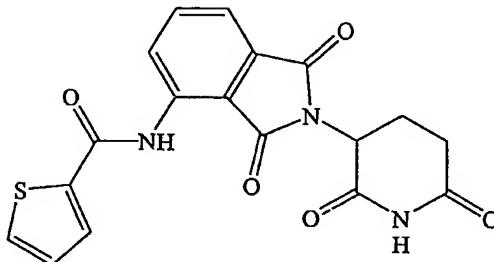
To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added pentanoyl chloride (0.48 g, 4.0 mmol). The stirred mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the
 35 resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.61 g (85 %) of

product as an off-white solid: mp 178-179 °C; ¹H NMR (DMSO-*d*₆) δ 11.17 (s, 1H), 9.65 (s, 1H), 8.50 (d, J=8.3 Hz, 1H), 7.82 (t, J=7.5 Hz, 1H), 7.59 (d, J=7.2 Hz, 1H), 5.18 (dd, J=5.0 and 12.4 Hz, 1H), 2.99-2.89 (m, 1H), 2.68-2.45 (m, 4H), 2.13-2.09 (m, 1H), 1.69-1.57 (m, 2H), 1.44-1.30 (m, 2H), 0.92 (t, J=7.2 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.72, 5 171.99, 169.73, 167.83, 166.64, 136.64, 136.07, 131.36, 125.96, 118.15, 116.68, 48.97, 36.32, 30.97, 26.88, 22.03, 21.70, 13.64; Anal. Calcd. For C₁₈H₁₉N₃O₅ : C, 60.50; H, 5.36; N, 11.76. Found: C, 60.10; H, 5.37; N, 11.58.

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]-2-thienylcarboxamide I-33

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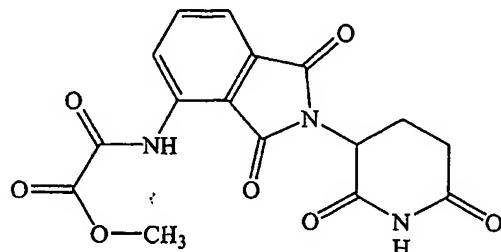


To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione 20 (0.55g, 2.0 mmol) in THF (30 ml) was added thiophene-2-carbonyl chloride (0.59 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. To the reaction mixture was added additional thiophene-2-carbonyl chloride (0.30 g, 2 mmol). The mixture was heated to reflux for an additional 8 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give an off-white solid which 25 was recrystallized from acetic acid to give 0.50 g (65 %) of product: mp 284-286 °C; ¹H NMR (DMSO-*d*₆) δ 11.19 (s, 1H), 10.34 (s, 1H), 8.47(d, J=8.3 Hz, 1H), 7.98-7.86 (m, 3H), 7.68 (d, J=7.3 Hz, 1H), 7.29 (dd, J=4.0 and 4.8 Hz, 1H), 5.19 (dd, J=5.4 and 12.6 Hz, 1H), 2.99-2.85 (m, 1H), 2.67-2.49(m, 2H), 2.12-2.08 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.72, 169.69, 167.96, 166.60, 159.67, 138.02, 136.26, 136.19, 133.26, 131.42, 129.91, 128.58, 30 126.42, 118.82, 117.94, 49.00, 30.93, 22.00; Anal. Calcd. For C₁₈H₁₃N₃O₅S : C, 55.77; H, 3.54; N, 10.60. Found: C, 55.67; H, 3.36; N, 10.42 + 0.2 AcOH + 0.05 H₂O.

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Methyl {N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]carbamoyl}formate I-34

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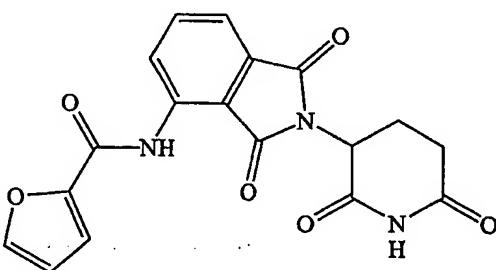


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- To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55g, 2.0 mmol) in THF (30 ml) was added methyl (chlorocarbonyl)formate (0.49 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.55 g
 15 (76 %) of product as an off-white solid: mp 247-249 °C; ¹H NMR (DMSO-*d*₆) δ 11.17 (s, 1H), 10.81 (s, 1H), 8.59 (d, J=8.3 Hz, 1H), 7.92 (t, J=7.7 Hz, 1H), 7.70 (d, J=7.3 Hz, 1H), 5.19 (dd, J=5.0 and 12.5 Hz, 1H), 3.91 (s, 3H), 2.98-2.85 (m, 1H), 2.68-2.50 (m, 2H), 2.14-2.09 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.70, 169.63, 168.03, 166.45, 159.81, 154.57, 136.65, 134.93, 131.36, 124.67, 119.34, 117.17, 53.80, 49.06, 30.92, 21.94; Anal. Calcd.
 20 For C₁₆H₁₃N₃O₇ : C, 53.49; H, 3.65; N, 11.70. Found: C, 53.53; H, 3.66; N, 11.52.

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]-2-furylcarboxamide I-35

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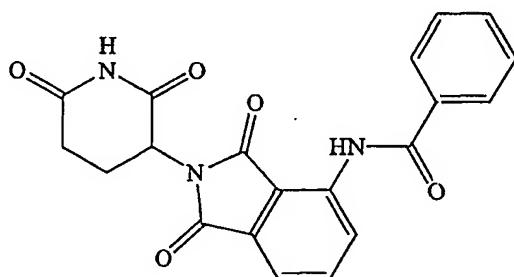
- To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added furan-2-carbonyl chloride (0.52 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. To the reaction mixture was added
 35 additional furan-2-carbonyl chloride (0.26 g, 2 mmol). The mixture was heated to reflux

for an additional 8 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.65 g (88 %) of product as an off-white solid: mp 299-301 °C; ¹H NMR (DMSO-*d*₆) δ 11.19 (s, 1H), 10.37 (s, 1H), 8.68 (dd, J=1.4 and 8.4 Hz, 1H), 8.06 (s, 1H), 7.90 (t, J=8.1 Hz, 1H), 7.65 (d, J=7.3 Hz, 1H), 7.39 (d, J=3.5 Hz, 1H), 6.79 (dd, J=1.5 and 3.2 Hz, 1H), 5.19 (dd, J=5.1 and 12.5 Hz, 1H), 2.98-2.84 (m, 1H), 2.67-2.49(m, 2H), 2.13-2.08 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.66, 169.62, 168.44, 166.59, 155.71, 146.80, 146.34, 136.55, 136.23, 136.12, 131.30, 124.86, 118.54, 116.64, 113.06, 48.98, 30.90, 22.01; Anal. Calcd. For C₁₈H₁₃N₃O₆ : C, 58.86; H, 3.57; N, 11.44. Found: C, 58.69; H, 3.54; N, 11.41.

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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]benzamide I-36

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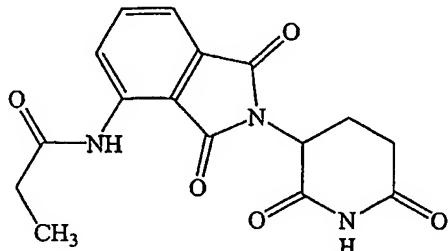
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To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added benzoyl chloride (0.56 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. To the reaction mixture was added additional benzoyl chloride (0.28 g, 2.0 mmol). The mixture was heated at reflux for an additional 8 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give an off-white solid which was recrystallized from acetic acid to give 0.49 g (65 %) of product: mp 268-270 °C; ¹H NMR (DMSO-*d*₆) δ 11.18 (s, 1H), 10.43 (s, 1H), 8.64-8.59 (m, 1H), 8.00-7.89 (m, 3H), 7.72-7.60 (m, 4H), 5.19 (dd, J=5.2 and 12.5 Hz, 1H), 2.98-2.84 (m, 1H), 2.66-2.50(m, 2H), 2.12-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.62, 169.59, 168.16, 166.64, 164.91, 136.50, 136.36, 133.23, 132.67, 131.36, 129.06, 127.24, 126.00, 118.74, 117.74, 48.98, 30.89, 21.98; Anal. Calcd. For C₂₀H₁₅N₃O₅ : C, 63.02; H, 4.08; N, 10.90. Found: C, 63.05; H, 4.06; N, 10.69 + 0.11 AcOH + 0.08 H₂O.

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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]propanamide I-37

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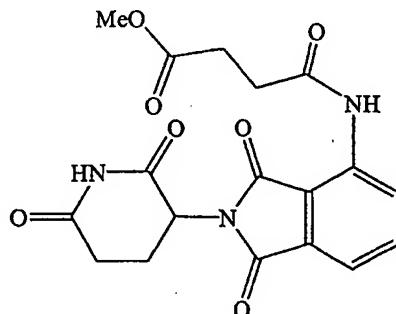
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To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added propanoyl chloride (0.37 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.58 g (88 %) of product as an off-white solid: mp 221-223 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 9.65 (s, 1H), 8.50 (d, J=8.3 Hz, 1H), 7.83 (t, J=7.6 Hz, 1H), 7.60 (d, J=7.2 Hz, 1H), 5.16 (dd, J=5.2 and 12.6 Hz, 1H), 2.99-2.85 (m, 1H), 2.66-2.45 (m, 4H), 2.11-2.07(m, 1H), 1.14 (t, J=7.5 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.69, 172.65, 169.71, 167.79, 166.62, 136.65, 136.09, 131.35, 125.93, 118.12, 116.66, 48.91, 30.91, 29.73, 21.97, 9.13; Anal. Calcd. For C₁₆H₁₅N₃O₅ : C, 58.36; H, 4.59; N, 12.76. Found: C, 58.01; H, 4.45; N, 12.61.

Methyl 3-{N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]carbamoyl}propanoate I-38

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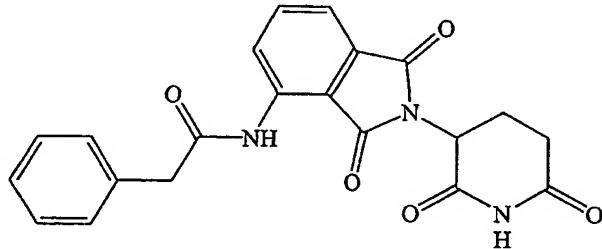
To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added methyl 3-(chlorocarbonyl)propanoate (0.63 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated

in vacuo and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.75 g (97 %) of product as an off-white solid: mp 224-226 °C; ¹H NMR (DMSO-*d*₆) δ 11.18 (s, 1H), 9.79 (s, 1H), 8.43 (d, J=8.4 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 7.62 (d, J=7.3 Hz, 1H), 5.16 (dd, J=5.2 and 12.6 Hz, 1H), 3.61 (s, 3H), 2.99-2.48 (m, 7H), 2.11-2.06 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.84, 172.66, 170.94, 169.75, 167.61, 166.70, 136.39, 136.15, 131.52, 126.39, 118.43, 117.04, 51.51, 48.95, 31.22, 30.96, 28.39, 22.03; Anal. Calcd. For C₁₈H₁₇N₃O₂: C, 55.82; H, 4.42; N, 10.85. Found: C, 55.68; H, 4.41; N, 10.61.

N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-phenylacetamide I-39

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To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 20 2.0 mmol) in THF (30 ml) was added 2-phenylacetyl chloride (0.62 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.72 g (92 %) of product as an off-white solid: mp 217-218 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 9.79 (s, 1H), 8.49 (d, J=8.4 Hz, 1H), 7.82 (t, J=7.9 Hz, 1H), 7.60 (t, J=7.3 Hz, 1H), 7.41-7.27 (m, 5H), 5.13 (dd, J=5.1 and 12.7 Hz, 1H), 3.85 (s, 2H), 2.98-2.83 (m, 1H), 2.64-2.44(m, 2H), 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.71, 170.07, 169.74, 167.60, 166.61, 136.38, 136.10, 134.70, 131.41, 129.41, 128.58, 126.97, 125.96, 118.39, 116.90, 48.89, 43.47, 30.90, 21.91; Anal. Calcd. For C₂₁H₁₇N₃O₅: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.23; H, 4.34; N, 10.53.

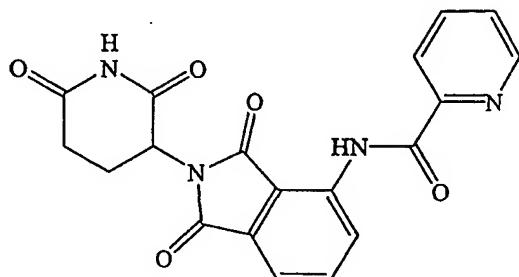
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N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-pyridylcarboxamide I-40

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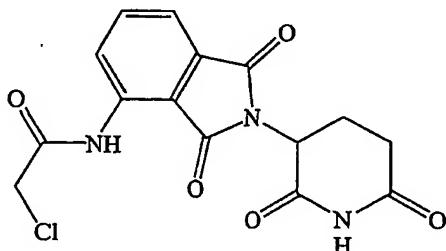


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To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2.0 mmol) in THF (30 ml) was added pyridine-2-carbonyl chloride hydrochloride (0.71 g, 4.0 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* and the resulting solid was slurried in a biphasic mixture of diethyl ether (20 ml)/20 % NH₄OH (20 ml) and filtered to give an off-white solid. The solid was re-slurried in methanol (20 ml) and filtered to give 0.30 g (40 %) of product: mp 336-338 °C; ¹H NMR (DMSO-*d*₆) δ 11.83 (s, 1H), 11.20 (s, 1H), 8.92 (d, J=8.4 Hz, 1H), 8.81 (d, J=3.6 Hz, 1H), 8.22 (d, J=7.7 Hz, 1H), 8.15 (t, J=7.4 Hz, 1H), 7.92 (t, J=7.7 Hz, 1H), 7.77-7.72 (m, 1H), 7.65 (d, J=7.2 Hz, 1H), 5.22 (dd, J=5.2 and 12.5 Hz, 1H), 3.00-2.86 (m, 1H), 2.69-2.52(m, 2H), 2.15-2.11 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.67, 169.67, 168.20, 166.61, 162.69, 148.83, 148.19, 138.45, 136.50, 136.16, 131.39, 127.72, 124.23, 122.46, 118.29, 116.32, 48.96, 30.91, 21.98; Anal. Calcd. For C₁₉H₁₄N₄O₅ : C, 60.32; H, 3.73; N, 14.81. Found: C, 60.05; H, 3.57; N, 14.45.

25 N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-chloroacetamide I-41

30



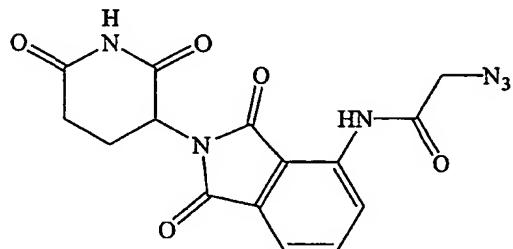
35

To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.37 g, 5.00 mmol) in THF (30 ml) was added chloroacetyl chloride (0.62 g, 5.5 mmol). The mixture was heated to reflux for 30 minutes. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 1.67 g (96 %) of product as an off-white solid: ¹H NMR (DMSO-*d*₆) δ 11.18 (s, 1H), 10.31 (s, 1H), 8.54 (d, J=8.4 Hz, 1H), 7.88 (t, J=7.7 Hz, 1H), 7.68 (d, J=7.3 Hz, 1H), 5.17(dd, J=5.2 and 12.7 Hz, 1H), 4.54 (s, 2H), 2.90-2.85 (m, 1H), 2.65-2.51 (m, 2H), 2.10-2.06(m, 1H).

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2-azido-N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]acetamide I-42

15



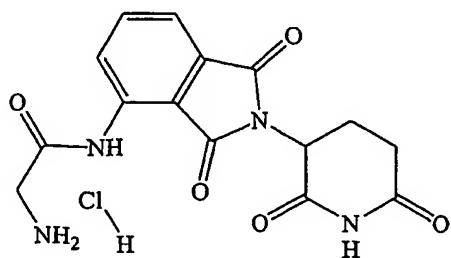
25

To a suspension of N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]-2-chloroacetamide (1.53 g, 4.4 mmol) in acetone (30 ml) was added sodium azide (0.43 g, 6.6 mmol). The mixture was heated to reflux for 18 hours. The solvent was evaporated *in vacuo* to give 1.49 g (96 %) of product as an off-white solid: ¹H NMR (DMSO-*d*₆) δ 11.19 (s, 1H), 10.20 (s, 1H), 8.49 (d, J=8.3 Hz, 1H), 7.88 (t, J=7.7 Hz, 1H), 7.68 (d, J=7.3 Hz, 1H), 5.17(dd, J=5.1 and 12.7 Hz, 1H), 4.34 (s, 2H), 2.99-2.84 (m, 1H), 2.65-2.47 (m, 2H), 2.09-2.00 (m, 1H).

30

2-Amino-N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]acetamide I-43, hydrochloride

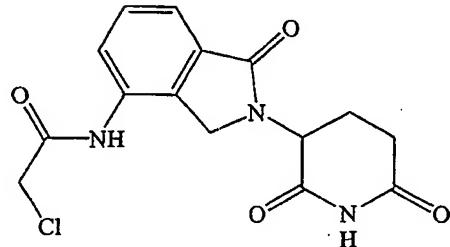
35



To a solution of 2-azido-N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]acetamide (1.49 g, 4.2 mmol) in methanol (50 ml) was added 10% Pd-C (0.1 g). Hydrogenation at 50 psi of hydrogen in a Parr Type shaker for 2 hours yielded a slurry. The mixture was filtered
 5 leaving a gray solid that was stirred in H₂O (50 ml). The pH of the aqueous mixture was adjusted to 4 by addition of 3N HCl. The aqueous mixture was filtered through celite to remove catalyst and the filtrate was stirred with 50 ml of ethyl acetate for 3 hours. The aqueous layer was separated and was evaporated *in vacuo* to give a solid which was slurried in ethyl acetate and filtered to give 0.72 g (45%) of product as an off-white solid: mp 305-
 10 307 °C; ¹H NMR (DMSO-*d*₆) δ 11.17 (s, 1H), 10.35 (s, 1H), 8.44 (bs, 3H), 8.32 (d, J=8.2 Hz, 1H), 7.90 (t, J=8.0 Hz, 1H), 7.71 (d, J=7.2 Hz, 1H), 5.16 (dd, J=5.1 and 12.6 Hz, 1H), 3.97 (s, 2H), 2.99-2.84 (m, 1H), 2.65-2.46 (m, 2H), 2.10-2.06(m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.81, 169.80, 166.75, 166.56, 166.19, 136.19, 134.91, 131.89, 127.62, 119.47, 118.68, 48.96, 41.13, 30.94, 22.00; Anal. Calcd. For C₁₅H₁₅ClN₄O₅: C, 48.62; H, 4.19; N,
 15 15.12. Found: C, 48.68; H, 4.18; N, 15.05 + 0.21 H₂O.

N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]-2-chloroacetamide I-44

20



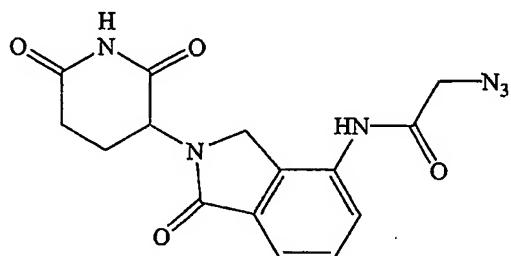
25

To a stirred suspension of 3-(4-amino-1-oxoisindolin-2-yl)piperidine-2,6-dione (3.89 g, 15.0 mmol) in THF (50 ml) was added chloroacetyl chloride (1.86 g, 16.5 mmol). The mixture was heated to reflux for 45 minutes. To the reaction mixture was added additional chloroacetyl chloride (0.15 g, 0.13 mmol). The reaction mixture was heated at
 30 reflux for an additional 30 minutes. The solvent was evaporated *in vacuo* and the resulting solid was slurried in diethyl ether (20 ml) and filtered to give 4.64 g (92 %) of product as an off-white solid: ¹H NMR (DMSO-*d*₆) δ 11.04 (s, 1H), 10.22 (s, 1H), 7.82 (dd, J=1.6 and 7.2 Hz, 1H), 7.59-7.50 (m, 2H), 5.16 (dd, J=5.1 and 13.2 Hz, 1H), 4.46-4.30 (m, 4H), 3.00-2.85 (m, 1H), 2.65-2.58 (m, 1H), 2.44-2.28 (m, 1H), 2.06-2.01 (m, 1H).

35

2-azido-N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]acetamide I-45

5

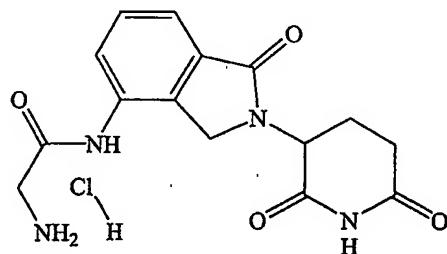


10 To a stirred suspension of N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]-2-chloroacetamide (4.64 g, 13.8 mmol) in acetone (60 ml) was added sodium azide (1.35 g, 20.7 mmol). The mixture was heated to reflux for 18 hours. After 18 hours, to the reaction mixture was added NaI (2.05 g, 13.8 mmol) and additional sodium azide (0.90 g, 13.8 mmol). The mixture was heated at reflux for an additional 18 hours. The solvent was
 15 evaporated *in vacuo* to give an off-white solid which was slurried in a mixture of dichloromethane (50 ml) and H₂O (50 ml). This slurry was filtered to give 4.39 g (93 %) of product: ¹H NMR (DMSO-*d*₆) δ 11.50-9.52 (bs, 2H), 7.87-7.84 (m, 1H), 7.59-7.50 (m, 2H), 5.17 (dd, J=5.0 and 13.1 Hz, 1H), 4.44 (d, J=17.6 Hz, 1H), 4.34 (d, J=17.6 Hz, 1H), 4.13 (s, 2H), 3.00-2.86 (m, 1H), 2.65-2.59 (m, 1H), 2.44-2.29 (m, 1H), 2.07-2.02 (m, 1H).

20

2-Amino-N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]acetamide I-46,
hydrochloride

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30

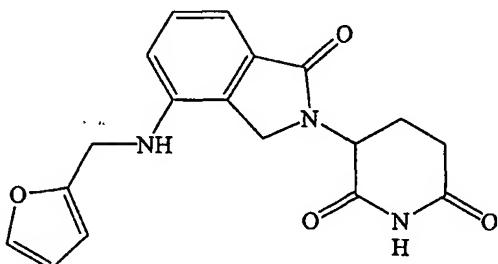
To a stirred suspension of 2-azido-N-[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]acetamide (1.49 g, 4.20 mmol) in a mixture of methanol (50 ml) and 3N HCl (6 ml) was added 10% Pd-C (0.1 g). Hydrogenation at 50 psi of hydrogen in a Parr Type shaker for 24 hours gave a slurry. The mixture was filtered leaving a gray solid that was stirred in H₂O
 35 (100 ml). The aqueous mixture was filtered through celite to remove catalyst. The aqueous

and methanolic filtrates were combined and evaporated *in vacuo* to give a white solid. The solid was slurried in ethyl acetate (20 ml), filtered, re-slurried in methanol (20 ml), and filtered to give 2.35 g (48 %) of product: mp 293-295 °C; ¹H NMR (DMSO-*d*₆) δ 11.06 (s, 1H), 10.86 (s, 1H), 8.45 (bs, 2H), 7.90 (d, J=6.3 Hz, 1H), 7.59-7.51 (m, 2H), 5.17 (dd, 5 J=4.9 and 13.0 Hz, 1H), 4.54 (d, J=17.8 Hz, 1H), 4.39 (d, J=17.8 Hz, 1H), 3.91 (s, 2H), 3.02-2.88 (m, 1H), 2.68-2.61 (m, 1H), 2.37-2.23 (m, 1H), 2.09-2.05 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.94, 171.07, 167.74, 165.24, 133.73, 132.86, 128.95, 125.01, 119.65, 51.59, 46.74, 40.90, 31.22, 22.82; Anal. Calcd. For C₁₅H₁₇ClN₄O₄: C, 50.43; H, 4.94; N, 15.68. Found: C, 50.08; H, 4.92; N, 15.53 + 0.25 H₂O.

10

3-{4-[(2-Furylmethyl)amino]-1-oxoisindolin-2-yl}piperidine-2,6-dione I-47

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20 To a stirred suspension of 3-(4-amino-1-oxoisindolin-2-yl)piperidine-2,6-dione (0.52 g, 2.0 mmol) in methanol (50 ml) was added furan-2-carbaldehyde (0.200 g, 2.05 mmol). The mixture was heated to reflux for 4 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in acetic acid (20 ml). Sodium triacetoxyborohydride (0.450 g, 2.05 mmol) was added to the reaction mixture. The reaction mixture was stirred 25 for 24 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (100 ml), washed with H₂O (3 × 100 ml), saturated aqueous NaHCO₃ (2 × 100 ml), brine (1 × 100 ml), and dried over MgSO₄. The solvent was evaporated *in vacuo* and the residue was partially purified by chromatography (100 % ethyl acetate) to give an off-white solid which was recrystallized from ethanol to give 0.20 g of product as a white solid: mp 248-250 °C; ¹H NMR (DMSO-*d*₆) δ 11.02 (s, 1H), 7.57 (s, 1H), 7.27 (t, J=7.6 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.36 (d, J=11.2 Hz, 2H), 6.22 (t, J=5.4 Hz, 1H), 5.12 (dd, J=4.9 and 13.1 Hz, 1H), 4.37 (d, J=5.5 Hz, 2H), 4.27 (d, J=17.2 Hz, 1H), 4.14 (d, J=17.2 Hz, 1H) 3.00-2.86 (m, 1H), 2.65-2.59 (m, 1H), 2.37-2.23 (m, 1H), 2.08-1.99 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.83, 171.16, 168.70, 152.82, 143.06, 142.00, 132.09,

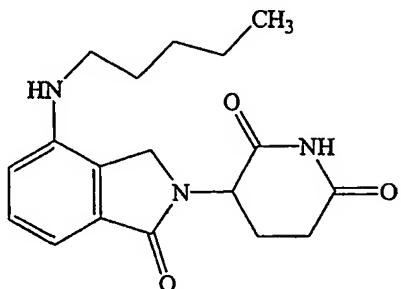
35

129.02, 126.76, 112.35, 110.63, 110.33, 107.08, 51.50, 45.73, 31.20, 22.75; Anal. Calcd. For C₁₈H₁₇N₃O₄ : C, 63.71; H, 5.05; N, 12.38. Found: C, 63.41; H, 5.03; N, 11.98.

3-[1-Oxo-4-(pentylamino)isoindolin-2-yl]piperidine-2,6-dione I-48

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10



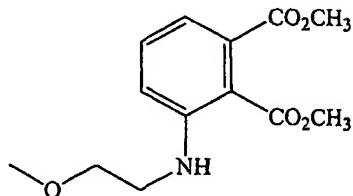
To a stirred solution of 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.52 g, 2.0 mmol) in DMF (10 ml) was added pentanal (0.26 g, 3.0 mmol), acetic acid (0.24 g, 4.0 mmol), and sodium triacetoxyborohydride (0.85 g, 4.0 mmol). The reaction mixture was stirred at room temperature for 6 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (100 ml), washed with H₂O (3 × 100 ml), brine (1 × 100 ml), and dried over MgSO₄. The solvent was evaporated and the residue was partially purified by chromatography (ethyl acetate/hexane, 75:25) to give an off-white solid which was slurried in ethyl acetate and filtered to give 0.14 g (21 %) of product as a white solid: mp 244-246 °C; ¹H NMR (DMSO-*d*₆) δ 11.00 (s, 1H), 7.28 (t, J=7.7 Hz, 1H), 6.92 (d, J=7.3 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 5.54 (t, J=5.3 Hz, 1H), 5.12 (dd, J=5.1 and 13.2 Hz, 1H), 4.24 (d, J=17.2 Hz, 1H), 4.13 (d, J=17.2 Hz, 1H) 3.15-3.07 (m, 2H), 3.00-2.86 (m, 1H), 2.65-2.59 (m, 1H), 2.39-2.23 (m, 1H), 2.08-1.99 (m, 1H), 1.61-1.57 (m, 2H), 1.41-1.32 (m, 4H), 0.89 (t, J=6.8 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.83, 171.19, 168.86, 143.74, 132.00, 129.15, 126.42, 111.66, 109.86, 51.46, 45.69, 42.68, 31.20, 28.80, 28.21, 22.79, 21.96, 13.89; Anal. Calcd. For C₁₈H₂₃N₃O₃ : C, 65.63; H, 7.04; N, 12.76. Found: C, 65.69; H, 7.22; N, 12.55.

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35

3-(2-Methoxy-ethylamino)-phthalic acid dimethyl ester

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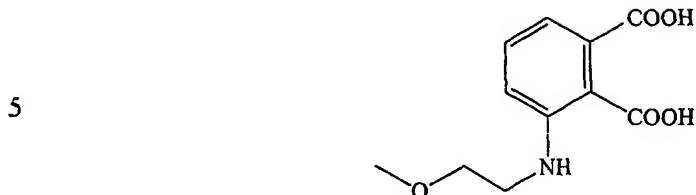


To a stirred solution of oxalyl chloride (1.75 ml, 20 mmol) in methylene chloride (20 ml)
 10 under a nitrogen atmosphere at -78°C was added DMSO (1.42 ml, 20 mmol) in methylene chloride (10ml) dropwise over 5 minutes. The mixture was stirred for 5 minutes followed by the dropwise addition of 2-methoxyethanol (1.58 ml, 20 mmol) in methylene chloride (10 ml) over 5 minutes. The mixture was stirred for 20 minutes followed by the dropwise addition of triethylamine (8.36 ml, 60 mmol) over 5 minutes. The resulting suspension was
 15 stirred for 30 minutes at -78°C and then allowed to warm to room temperature. The reaction mixture was diluted with methylene chloride (20 ml). To this stirred mixture was added 3-amino-phthalic acid dimethyl ester (2.09 g, 10 mmol) and acetic acid (4.60 ml, 80 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 5 minutes followed by the addition of sodium triacetoxyborohydride (4.24 g, 20 mmol). The
 20 mixture was stirred for 3 h. The reaction mixture was diluted with methylene chloride (50 ml) and washed with water (3x100 ml), saturated aqueous sodium bicarbonate (2x100 ml), brine (100 ml), and dried (MgSO_4). The solvent was evaporated *in vacuo* and the residue purified by chromatography (25% ethyl acetate/hexane) to give 2.24 g (84%) of product as an oil. $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 7.32 (t, $J=8.0$ Hz, 1H), 6.88-6.79 (m, 3H), 3.85 (s, 3H), 3.83
 25 (s, 3H), 3.62 (t, $J=5.4$ Hz, 2H), 3.41 (s, 3H), 3.35 (q, $J=5.2$ Hz, 2H).

30

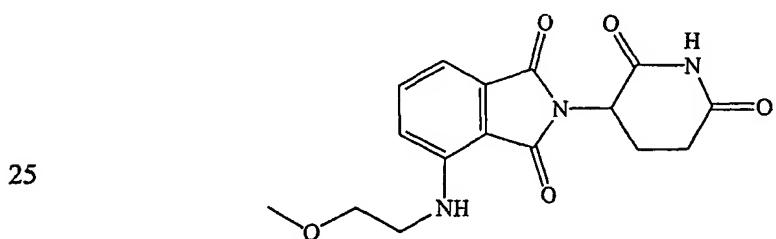
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3-(2-Methoxy-ethylamino)-phthalic acid



To a stirred solution of 3-(2-methoxy-ethylamino)-phthalic acid dimethyl ester (2.24 g, 8.38 mmol) in methanol (50 ml) was added 5N potassium hydroxide (10 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue dissolved in water (50 ml). The water was washed with diethyl ether (2 x 75 ml). The aqueous portion was cooled in an ice bath and the pH was adjusted to 2-3 by dropwise addition of concentrated hydrochloric acid. The aqueous solution was then extracted with ethyl acetate (3 x 75 ml). The combined ethyl acetate extracts were washed with brine (100 ml) and dried (MgSO_4). The solvent was evaporated *in vacuo* and the residue, which contained a mixture of diacid and monomethyl esters, was used without further purification.

20 2-(2,6-Dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione I-49

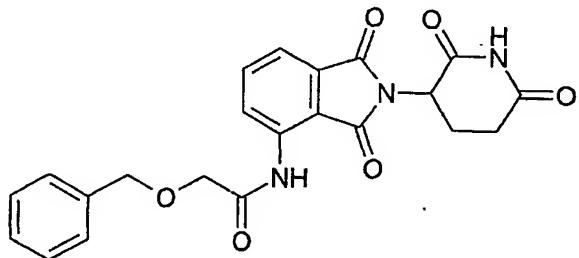


To a stirred solution of 3-(2-methoxy-ethylamino)-phthalic acid (8.38 mmol) in
 30 pyridine (40 ml) was added 3-amino-piperidine-2,6-dione hydrochloride (1.39 g, 8.42
 mmol). The reaction mixture was heated to reflux for 5 hours. The solvent was evaporated
 in *vacuo* and the residue dissolved in methylene chloride (125 ml). The methylene chloride
 mixture was treated with Norit (2 g), washed with water (2 x 100 ml), 0.1N HCl (1 x 100
 ml), brine (1 x 100 ml), and dried (MgSO_4). The solvent was evaporated in *vacuo* and the
 35 residue (oil) crystallized from a minimal amount of ethanol to give a yellow solid that was

purified by preparative HPLC to give 1.71 g (64%) of product as a yellow solid: mp 182-184°C; ¹H NMR (DMSO-*d*₆) δ 11.12 (s, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 7.04 (d, J=6.9 Hz, 1H), 6.59 (bs, 1H), 5.07 (dd, J=4.7 and 12.1 Hz, 1H), 3.54-3.30 (m, 7H), 2.95-2.85 (m, 1H), 2.64-2.52 (m, 2H), 2.07-2.02 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.79, 5
170.06, 168.98, 167.27, 146.38, 136.21, 132.07, 117.33, 110.67, 109.24, 70.39, 58.12, 48.58, 41.50, 30.99, 22.15; Anal. Calcd. For C₁₆H₁₇N₃O₅: C, 58.00; H, 5.17; N, 12.68. Found: C, 58.06; H, 5.12; N, 12.76.

2-Benzyl-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-10 acetamide I-50

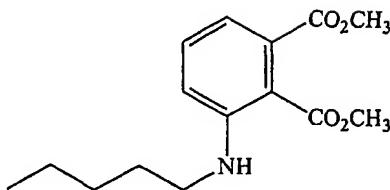
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To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.10 g, 4
20 mmol) in THF (30 ml) was added benzylxycetyl chloride (1.26 ml, 8 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* and the residue was slurried in diethyl ether (30 ml), filtered, recrystallized from a minimal amount of acetic acid, slurried in ethyl acetate (15 ml), and filtered to give 1.35 g
25 (80%) of product: mp 204-206 °C; ¹H NMR (DMSO-*d*₆) δ 11.20 (s, 1H), 10.40 (s, 1H), 8.71 (d, J=8.4 Hz, 1H), 7.86 (t, J=7.9 Hz, 1H), 7.64 (d, J=7.2 Hz, 1H), 7.50-7.28 (m, 5H), 5.17 (dd, J=5.0 and 12.5 Hz, 1H), 4.72 (s, 2H), 4.21 (s, 2H), 2.99-2.85 (m, 1H), 2.67-2.51 (m, 2H), 2.12-2.08 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.78, 169.78, 169.01, 168.27, 166.67, 137.04, 136.52, 135.93, 131.29, 128.36, 127.82, 124.40, 118.38, 116.08, 72.78,
30 69.23, 48.97, 30.92, 21.98; Anal. Calcd. For C₂₂H₁₉N₃O₆: C, 62.70; H, 4.54; N, 9.97. Found: C, 62.77; H, 4.54; N, 9.82.

3-Pentylamino-phthalic acid dimethyl ester

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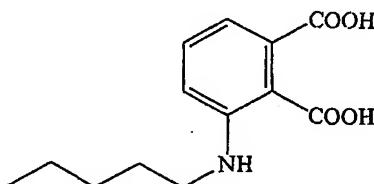


To a stirred solution of 3-amino-phthalic acid dimethyl ester (3.14 g, 15 mmol) in methylene chloride (50 ml) under a nitrogen atmosphere were added valeraldehyde (2.0 ml, 10 18.75 mmol) and acetic acid (5.18 ml, 90 mmol). The mixture was stirred for 5 minutes followed by addition of sodium triacetoxyborohydride (6.36g, .30 mmol). The reaction was stirred for 30 minutes, diluted with methylene chloride (50 ml), washed with water (2 x 100 ml), saturated aqueous sodium bicarbonate (2 x 100 ml), brine (100 ml), and dried (MgSO_4). The solvent was evaporated *in vacuo* to give 4.19 g of product (100%) that used 15 without further purification. ^1H NMR ($\text{DMSO}-d_6$) δ 7.31 (t, $J=7.9$ Hz, 1H), 6.81-6.75 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.15 (bs, 2H), 1.68-1.60 (m, 2H), 1.45-1.32 (m, 4H), 0.89 (t, $J=6.9$ Hz, 3H).

20

3-Pentylamino-phthalic acid

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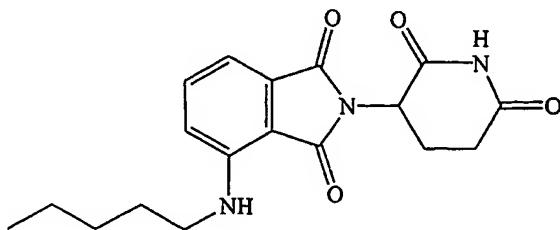
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3-Pentylamino-phthalic acid dimethyl ester (4.19, 15 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

35

2-(2,6-Dioxo-piperidin-3-yl)-4-pentylamino-isoindole-1,3-dione I-51

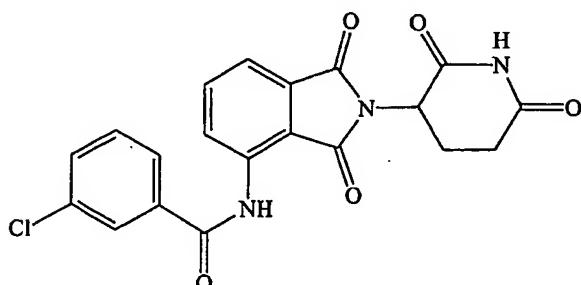
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To a stirred solution of 3-pentylamino-phthalic acid (2.51 g, 10 mmol) in acetic acid (50 ml) was added 3-amino-piperidine-2,6-dione hydrochloride (1.81 g, 11 mmol). The reaction mixture was heated to reflux overnight. The solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate (100 ml). The ethyl acetate mixture was washed with water (2 x 100 ml), saturated aqueous sodium bicarbonate (2 x 100 ml), brine (1 x 100 ml), and dried (MgSO_4). The solvent was evaporated *in vacuo* and the solid residue was purified by chromatography (25% ethyl acetate/hexane) to give 1.82 g (53%) of product as a yellow solid: mp 141-143 °C; ¹H NMR (DMSO-*d*₆) δ 11.09 (s, 1H), 7.58 (t, J=8.3 Hz, 1H), 7.08 (d, J=8.6 Hz, 1H), 7.02 (d, J=7.0 Hz, 1H), 6.519 (t, J=5.7 Hz, 1H), 5.06 (dd, J= 5.3 and 12.4 Hz, 1H), 3.32-3.25 (m, 2H), 2.97-2.82 (m, 1 H), 2.62-2.46 (m, 2H), 2.06-2.01 (m, 1H), 1.61-1.55 (m, 2H), 1.35-1.32 (m, 4H), 0.88 (t, J=6.7 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.72, 170.01, 168.92, 167.25, 146.39, 136.21, 132.14, 117.08, 110.31, 108.99, 48.52, 41.77, 30.94, 28.46, 28.33, 22.12, 21.82, 13.85; Anal. Calcd. For $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.92; H, 6.17; N, 12.15.

25 3-Chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide I-52

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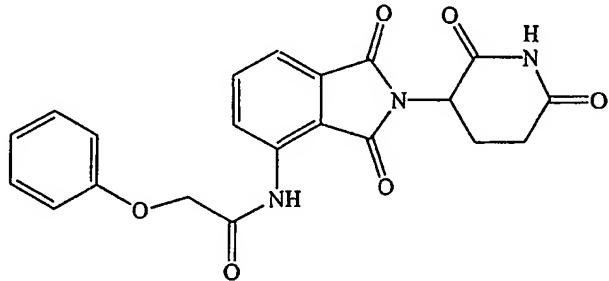


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To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added 3-chlorobenzoyl chloride (0.51 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated
5 *in vacuo* leaving a solid which was slurried in diethyl ether (20 ml) and filtered to give 0.82 g (100%) of product as an off-white solid: mp 257-259 °C; ¹H NMR (DMSO-*d*₆) δ 11.06 (s, 1H), 10.43 (s, 1H), 8.50 (d, J=8.4 Hz, 1H), 7.99-7.88 (m, 3H), 7.75-7.61 (m, 3H), 5.17 (dd, J=5.5 and 12.7 Hz, 1H), 2.99-2.84 (m, 1H), 2.67-2.49 (m, 2H), 2.12-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.36, 169.78, 169.36, 167.59, 166.39, 163.57, 135.99, 135.31,
10 133.59, 132.11, 131.33, 130.73, 127.07, 126.76, 125.78, 118.93, 118.55, 48.91, 30.77, 21.85; Anal. Calcd. For C₂₀H₁₄ClN₃O₅ : C, 58.33; H, 3.43; N, 10.20. Found: C, 58.38; H, 3.23; N, 9.95.

N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-phenoxy-
15 acetamide I-53

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25 To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added phenoxyacetyl chloride (0.55 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid which was slurried in diethyl ether (20 ml) and filtered to give 0.76 g (93%)
30 of product as an off-white solid: mp 236-238 °C; ¹H NMR (DMSO-*d*₆) δ 11.19 (s, 1H), 10.53 (s, 1H), 8.73 (d, J=8.4 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 7.64 (d, J=7.3 Hz, 1H), 7.38 (t, J=7.6 Hz, 2H) 7.14-7.01 (m, 3H), 5.21 (dd, J=5.3 and 12.6 Hz, 1H), 4.81 (s, 2H), 3.00-2.86 (m, 1H), 2.67-2.51 (m, 2H), 2.13-2.09 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.77, 169.77, 168.37, 167.59, 166.67, 156.85, 136.58, 135.84, 131.28, 129.74, 124.45, 121.91,

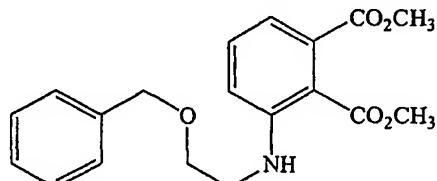
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118.50, 116.28, 114.86, 67.03, 49.02, 30.96, 21.93; Anal. Calcd. For C₂₁H₁₇N₃O₆: C, 61.92; H, 4.21; N, 10.31. Found: C, 61.87; H, 4.27; N, 10.25.

3-(2-Benzylamino)-phthalic acid dimethyl ester

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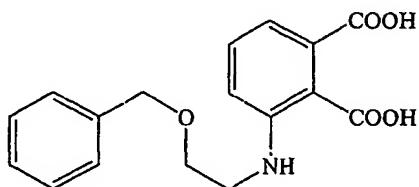
Benzylxycetaldehyde (5.27 ml, 37.5 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The residue (oil)

was purified by chromatography (6:3:1 methylene chloride/hexane/ethyl acetate) to give 7.98 g (78%) of yellow oil: ¹H NMR (DMSO-d₆) δ 7.38-7.26 (m, 5H), 6.89-6.77 (m, 3H),

15 4.57 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.69 (t, J=5.5 Hz, 2H), 3.38 (q, J=5.4 Hz, 2H).

3-(2-Benzylamino)-phthalic acid

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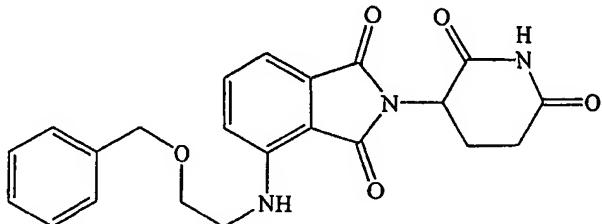
25 3-(2-Benzylamino)-phthalic acid dimethyl ester (2.50 g, 7.28 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

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4-(2-Benzylxyloxy-ethylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione I-54

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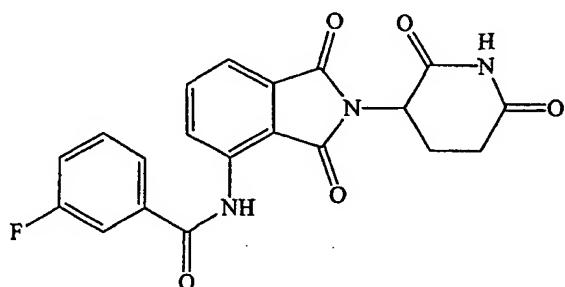


- 10 3-(2-Benzylxyloxy-ethylamino)-phthalic acid (1.78 g, 5.65 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-Dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione. The solid yellow residue was recrystallized from a minimal amount of ethanol to give 1.32 g (57%) of product as a yellow solid: mp 158-160 °C; ¹H NMR (DMSO-*d*₆) δ 11.11 (s, 1H), 7.57 (t, J=7.3 Hz, 1H), 7.37-7.24 (m, 5H), 7.14 (d, J=8.6 Hz, 1H), 7.04 (d, J=7.0 Hz, 1H), 6.67 (t, J=5.7 Hz, 1H), 5.07 (dd, J= 5.4 and 12.5 Hz, 1H), 4.54 (s, 2H), 3.66-3.62 (m, 2H), 3.55-3.49 (m, 2H), 2.97-2.82 (m, 1 H), 2.63-2.45 (m, 2H), 2.06-2.02 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.81, 170.08, 168.96, 167.28, 146.40, 138.23, 136.16, 132.06, 128.22, 127.42, 117.47, 110.69, 109.30, 71.90, 68.09, 48.54, 41.68, 30.97, 22.13; Anal. Calcd. For C₂₂H₂₁N₃O₅: C, 64.86; H, 5.20; N, 10.31.
- 15 20 Found: C, 64.95; H, 5.03; N, 10.27.

N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-benzamide I-55

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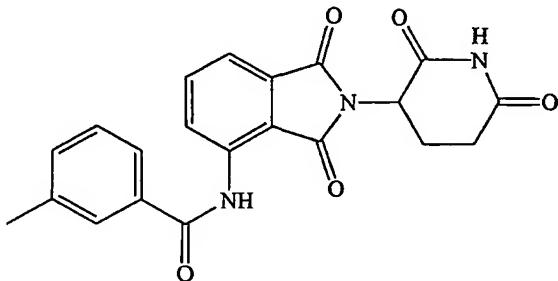


- To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added 3-Fluorobenzoyl chloride (0.49 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature,

methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid which was slurried in diethyl ether (20 ml) and filtered to give 0.69 g (96%) of product as an off-white solid: mp 260-262 °C; ¹H NMR (DMSO-*d*₆) δ 11.00 (s, 1H), 10.39 (s, 1H), 8.53 (d, J=8.3 Hz, 1H), 7.94-7.50 (m, 6H), 5.15 (dd, J=5.6 and 12.7 Hz, 1H), 2.97-2.83 (m, 1H), 2.66-2.49 (m, 2H), 2.14-2.06 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.36, 169.36, 167.66, 166.39, 163.62, 136.03, 131.31, 131.12, 130.99, 126.60, 123.19, 123.15, 119.44, 119.11, 118.89, 118.42, 114.31, 113.94, 48.91, 30.77, 21.83; Anal. Calcd. For C₂₀H₁₄FN₃O₅: C, 60.76; H, 3.57; N, 10.63. Found: C, 60.88; H, 3.38; N, 10.51.

10 N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methyl-benzamide I-56

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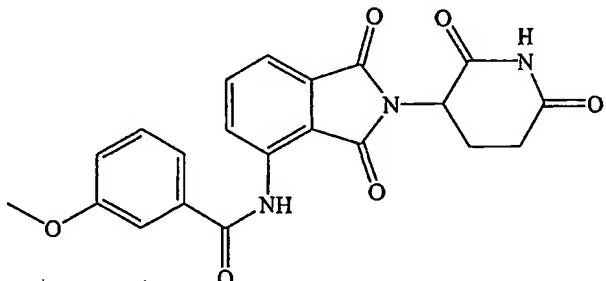
To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added *m*-toluoyl chloride (0.53 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid that was slurried in diethyl ether (20 ml), filtered, reslurried in ethyl acetate (20 ml), and filtered to give 0.69 g (88%) of product as an off-white solid: mp 234-236 °C; ¹H NMR (DMSO-*d*₆) δ 10.97 (s, 1H), 10.31 (s, 1H), 8.64(d, J=8.4 Hz, 1H), 7.92-7.47 (m, 6H), 5.16 (dd, J=5.5 and 12.7 Hz, 1H), 2.97-2.84 (m, 1H), 2.68-2.43 (m, 5H), 2.14-2.09 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.13, 169.15, 168.03, 166.30, 164.80, 138.18, 136.54, 135.95, 133.14, 132.87, 131.09, 128.57, 127.45, 126.64, 123.95, 118.23, 117.33, 48.88, 30.67, 21.76, 20.62; Anal. Calcd. For C₂₁H₁₇N₃O₅: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.23; H, 4.18; N, 10.56.

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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-benzamide I-57

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To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added *m*-anisoyl chloride (0.56 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid that was slurried in diethyl ether (20 ml), filtered, reslurried in ethyl acetate (20 ml), filtered, and recrystallized from minimal acetic acid to give 0.51 g (63%) of product as an off-white solid: mp 240-242 °C; ¹H NMR (DMSO-*d*₆) δ 11.15 (s, 1H), 10.38 (s, 1H), 8.60 (d, J=8.3 Hz, 1H), 7.91 (t, J=7.5 Hz, 1H), 7.67 (d, J=7.2 Hz, 1H), 7.55-7.50 (m, 3H), 7.29-7.22 (m, 1H), 5.19 (dd, J=5.3 and 12.5 Hz, 1H), 3.86 (s, 3H), 2.99-2.84 (m, 1H), 2.66-2.50 (m, 2H), 2.12-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.02, 169.71, 168.12, 166.64, 164.70, 159.56, 136.52, 136.31, 134.73, 131.36, 130.26, 126.18, 119.19, 118.78, 118.26, 117.92, 112.74, 55.41, 48.97, 30.93, 21.99; Anal. Calcd. For C₂₁H₁₇N₃O₆: C, 59.73; H, 4.46; N, 9.29. Found: C, 59.37; H, 4.34; N, 9.10 + 0.75 AcOH.

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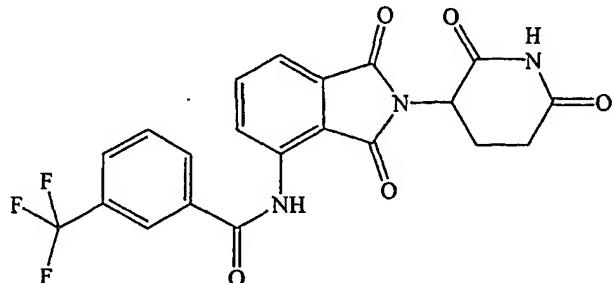
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-trifluoromethyl-benzamide I-58

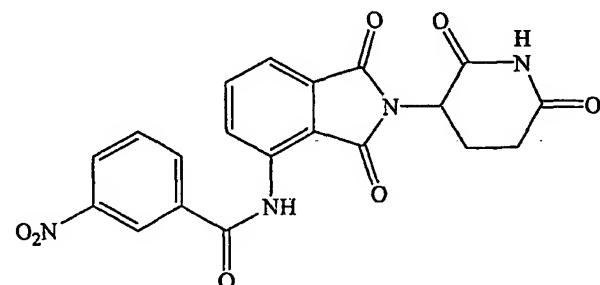
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- To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added 3-trifluoromethylbenzoyl chloride (0.60 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid that was slurried in diethyl ether (20 ml) and filtered to give 0.41 g (46%) of product as an off-white solid: mp 257-259 °C; ¹H NMR (DMSO-*d*₆) δ 10.86 (s, 1H), 10.45 (s, 1H), 8.50 (d, J=8.5 Hz, 1H), 8.24-8.25 (m, 2H), 8.02-7.82 (m, 3H), 7.69 (d, J=7.3 Hz, 1H), 5.14 (dd, J=5.7 and 12.8 Hz, 1H), 2.95-2.82 (m, 1H), 2.67-2.48 (m, 2H), 2.14-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 171.75, 168.80, 167.31, 166.06, 163.43, 135.80, 135.60, 134.28, 131.16, 130.71, 129.75, 128.35, 128.29, 126.63, 123.59, 123.52, 118.65, 118.55, 48.84, 30.51, 21.62; Anal. Calcd. For C₂₁H₁₄F₃N₃O₅: C, 56.64; H, 3.17; N, 9.44. Found: C, 56.48; H, 3.15; N, 9.41.
- 25 N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-nitro-benzamide I-59

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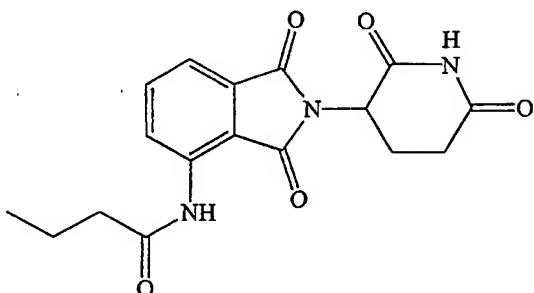
- To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.10 g, 4 mmol) in THF (30 ml) was added 3-nitrobenzoyl chloride (1.48 g, 8 mmol). The mixture

was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid that was slurried in diethyl ether (30 ml) and filtered to give 1.60 g (95%) of product as an off-white solid: mp 245-247 °C; ¹H NMR (DMSO-*d*₆) δ 10.85 (s, 1H), 10.53 (s, 1H), 8.76 (s, 1H), 8.50-8.37 (m, 3H), 7.95-7.87 (m, 2H), 7.70 (d, J=7.4 Hz, 1H), 5.14 (dd, J=5.7 and 12.7 Hz, 1H), 3.02-2.83 (m, 1H), 2.67-2.47 (m, 2H), 2.15-2.07 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 171.73, 168.79, 167.19, 166.04, 162.85, 147.84, 135.60, 134.79, 132.92, 131.21, 130.19, 126.87, 126.20, 121.69, 118.83, 48.86, 30.51, 21.63; Anal. Calcd. For C₂₀H₁₄N₄O₇: C, 56.88; H, 3.34; N, 13.27. Found: C, 56.87; H, 3.33; N, 13.05.

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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-butyramide I-60

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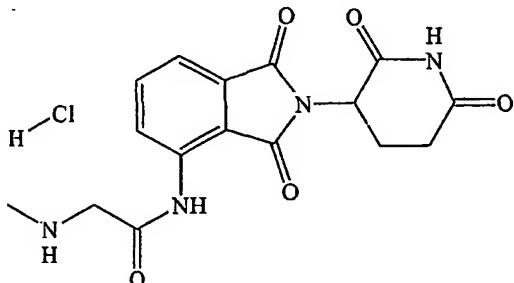
To a suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.55 g, 2 mmol) in THF (30 ml) was added butanoyl chloride (0.42 ml, 4 mmol). The mixture was heated to reflux for 18 hours. The reaction was cooled to room temperature, methanol (2 ml) was added, and the mixture stirred for 1 hour. The solvent was evaporated *in vacuo* leaving a solid that was slurried in diethyl ether (20 ml) and filtered to give 0.55 g (80%) of product as an off-white solid: mp 171-173 °C; ¹H NMR (DMSO-*d*₆) δ 11.14 (s, 1H), 9.68 (s, 1H), 8.48 (d, J=8.3 Hz, 1H), 7.83 (t, J=7.5 Hz, 1H), 7.61 (d, J=7.2 Hz, 1H), 5.15 (dd, J=5.2 and 12.6 Hz, 1H), 2.96-2.84 (m, 1H), 2.65-2.42 (m, 4H), 2.11-2.06 (m, 1H), 1.73-1.58 (m, 2H), 0.95 (t, J=7.4 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.70, 171.84, 169.72, 167.70, 166.63, 136.54, 136.07, 131.41, 126.17, 118.23, 116.89, 48.90, 30.91, 21.96, 18.25, 13.46; Anal. Calcd. For C₁₇H₁₇N₃O₅: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.45; H, 4.82; N, 12.15.

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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylamino-acetamide hydrochloride I-61

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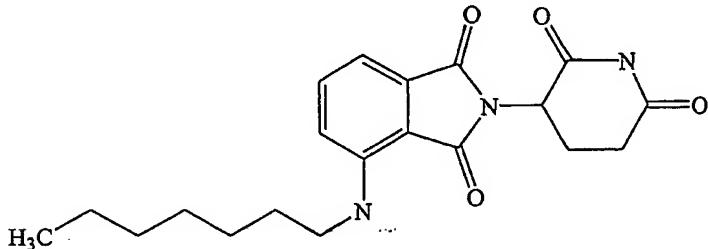


To a suspension of N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-chloroacetamide (0.95 g, 2.72 mmol) in THF (30 ml) was added sodium iodide (0.41 g, 2.72 mmol) and 2M methyl amine in THF (4.08 ml, 8.15 mmol). The mixture was stirred at room temperature for 5 hours. The solvent was evaporated *in vacuo* leaving a white solid. The solid was slurried in ethyl acetate (200 ml) for 2 h. The suspension was then washed with water (3 x 100 ml), brine (100 ml), and dried (MgSO_4). The solvent was evaporated *in vacuo* leaving an off-white solid. The solid was dissolved in acetonitrile (20 ml) and to this solution was added 2M HCl in ether (2 ml). The mixture was stirred for 1 h and the solvent evaporated *in vacuo*. The residue was slurried in ethyl acetate for 3 h and filtered to give an off-white solid. The solid was dissolved in water (40 ml) and washed with ethyl acetate (2 x 50 ml). The pH of the aqueous portion was adjusted to 11-12 by dropwise addition of saturated aqueous sodium carbonate. The aqueous mixture was washed with ethyl acetate (3 x 100 ml). The combined ethyl acetate extracts were washed with brine (100 ml), and dried (MgSO_4). The solvent was evaporated *in vacuo* leaving a white solid. The solid was dissolved in acetonitrile (15 ml) and 2M HCl in ether (2 ml) was added to the solution. The mixture was stirred for 1 h and the solvent was evaporated *in vacuo* leaving a white solid. The solid was slurried in diethyl ether (20 ml) and filtered to give 0.18 g (17 %) of product as a white solid: mp 228-230 °C; ^1H NMR ($\text{DMSO}-d_6$) δ 11.13 (s, 1H), 10.50 (s, 1H), 9.35 (bs, 2H), 8.28-8.21 (m, 1H), 7.93-7.63 (m, 2H), 5.15 (dd, $J=5.1$ and 12.6 Hz, 1H), 4.09 (s, 2H), 3.03-2.85 (m, 1H), 2.63-2.47 (m, 5H), 2.10-2.05 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 171.99, 169.03, 166.35, 166.07, 164.75, 135.63, 134.46, 131.56, 127.45, 119.14, 118.85, 49.56, 48.82, 32.49, 30.59, 21.69; Anal. Calcd. For $\text{C}_{16}\text{H}_{17}\text{ClN}_4\text{O}_5$: C, 48.99; H, 4.70; N, 14.28. Found: C, 48.82; H, 4.72; N, 14.02 + 0.64 H_2O .

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2-(2,6-Dioxo-piperidin-3-yl)-4-heptylamino-isoindole-1,3-dione I-62

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A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and heptanal (3.4 mL, 24 mmol) and acetic acid (2 mL) in DMF (20 mL) was heated until all solid was dissolved. To the mixture was added sodium borohydride (605 mg, 16 mmol) and kept at room temperature for 18h. To the mixture was added sodium borohydride (150 mg, 3.9 mmol) and kept at room temperature for 1 d. The mixture was extracted with ethyl acetate (200 mL) and water (100 mL). The organic layer was washed with water (100 mL). The solvent was removed *in vacuo* to give an oil. The oil was purified by column chromatography (Silica Gel, 33% EtOAc:CH₂Cl₂) to give 2-(2,6-Dioxo-piperidin-3-yl)-4-heptylamino-isoindole-1,3-dione as a yellow solid (610 mg, 41% yield):

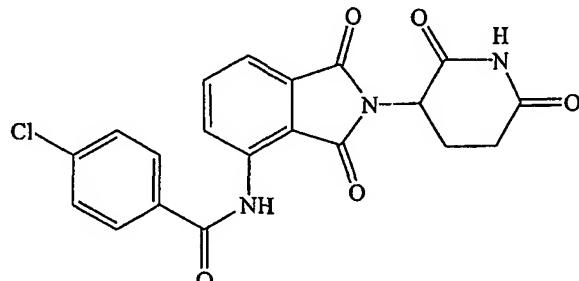
15 mp, 107-109 °C; ¹H NMR (DMSO-d6) δ 0.82-0.87 (m, 3H, CH₃), 1.24-1.29 (m, 8H, 4 CH₂), 2.00-2.04 (m, 1H, CHH), 2.43-2.62 (m, 2H, CH₂), 2.82-2.96 (m, 1H, CHH), 3.23-3.31 (m, 2H, CH₂), 5.06 (dd, *J* = 5.3, 12.4 Hz, 1H, NCH), 6.51 (t, *J* = 5.9 Hz, 1H, NH), 7.01 (d, *J* = 7.0 Hz, 1H, Ar), 7.07 (d, *J* = 8.6 Hz, 1H, Ar), 7.57 (dd, *J* = 7.4, 8.4 Hz, 1H, Ar), 11.10 (s, 1H, NH); ¹³C NMR (DMSO-d6) δ 13.91, 22.03, 22.17, 26.28, 28.42, 28.69, 30.98, 31.22, 34.84, 48.55, 109.03, 110.36, 117.13, 132.18, 136.24, 146.43, 167.29, 168.96, 170.05, 172.77; Anal Calcd for C₂₀H₂₅N₃O₄: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.62; H, 6.76; N, 11.13.

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4-Chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide I-63

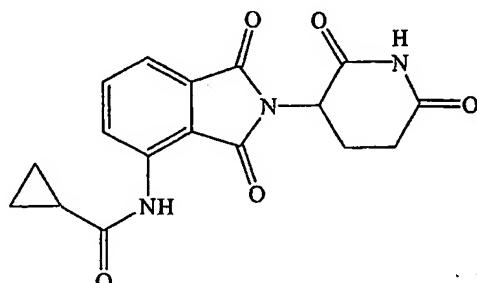
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- A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.2 g, 4.5 mmol) and 4-chlorobenzoyl chloride (1.1 mL, 8.8 mmol) in THF (40 mL) was heated to reflux for 15 h. To the mixture was added methanol (5 mL) to give a suspension. The 15 suspension was filtered and washed with ether (2 x 10 mL) then methanol (5 mL) to give 4-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide as a white solid (1.5 g, 81 % yield): mp, 261-263 °C; ¹H NMR (DMSO-d₆) δ 2.05-2.09 (m, 1H, CHH), 2.49-2.65 (m, 2H, CH₂), 2.83-2.98 (m, 1H, CHH), 5.18 (dd, *J* = 5.5, 12.8 Hz, 1H, NCH), 7.68-7.72 (m, 3H, Ar), 7.89-8.01 (m, 3H, Ar), 8.52 (d, *J* = 8.2, Hz, 1H, Ar), 10.47 (s, 1H, NH), 11.16 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 21.99, 30.92, 48.98, 118.48, 119.06, 126.76, 129.10, 129.29, 131.46, 132.13, 136.28, 137.47, 164.08, 166.60, 167.86, 169.67, 172.72; Anal Calcd for C₂₀H₁₄N₃O₅Cl + 0.2 H₂O: C, 57.83; H, 3.49; N, 10.12; Cl, 8.53; H₂O, 0.87. Found: C, 57.88; H, 3.33; N, 9.93; Cl, 8.53; H₂O, 0.73.
- 20 25 Cyclopropanecarboxylic acid [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide I-64

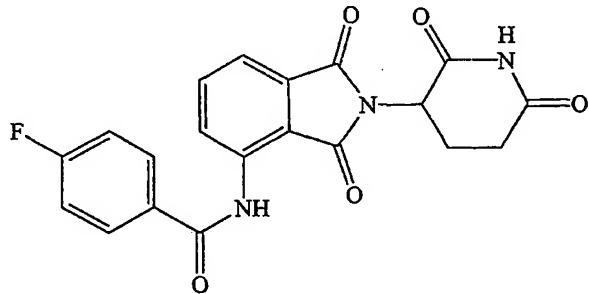
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- A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.60 g, 2.2 mmol) and cyclopropanecarbonyl chloride (0.4 mL, 4.4 mmol) in THF (20 mL) was heated to reflux for 15 h. To the mixture was added methanol (5 mL). The solvent was removed *in vacuo* to give a solid. The solid was slurried in ether (30 mL) for 1 h. The suspension
 5 was filtered and washed with ether (30 mL) to give cyclopropanecarboxylic acid [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide as a solid (630 mg, 84 % yield): mp, 237-239 °C; ¹H NMR (DMSO-d₆) δ 0.87-0.90 (m, 4H, 2CH₂), 1.93-2.09 (m, 2H, CH, CHH), 2.49-2.65 (m, 2H, CH₂), 2.64-2.96 (m, 1H, CHH), 5.15 (dd, *J* = 5.2, 12.6 Hz, 1H, NCH), 7.61 (d, *J* = 7.2 Hz, 1H, Ar), 7.82 (t, *J* = 7.7 Hz, 1H, Ar), 8.41 (d, *J* = 8.3 Hz, 1H, Ar), 9.99 (s, 1H, NH), 11.16 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 8.10, 14.93, 22.00, 30.93, 48.92, 117.07, 118.30, 126.69, 131.49, 135.97, 136.43, 166.67, 167.57, 169.77, 172.55, 172.74; Anal Calcd for C₁₇H₁₅N₃O₅: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.50; H, 4.39; N, 12.04.
- 10 15 N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-fluoro-benzamide I-65

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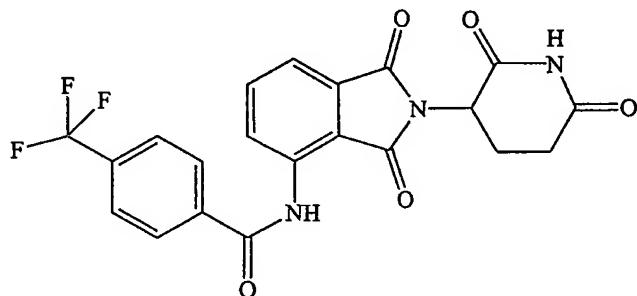


- 25 A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and 4-fluorobenzoyl chloride (0.95 mL, 8.0 mmol) in THF (40 mL) was heated to reflux for 15 h. To the mixture was added methanol (5 mL) to give a suspension. The suspension was filtered and washed with ether (2 x 10 mL) then methanol (5 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-fluoro-benzamide
 30 as a yellow solid (1.2 g, 77 % yield): mp, 283-285 °C; ¹H NMR (DMSO-d₆) δ 2.06-2.10 (m, 1H, CHH), 2.48-2.65 (m, 2H, CH₂), 2.83-2.97 (m, 1H, CHH), 5.18 (dd, *J* = 5.4, 12.6 Hz, 1H, NCH), 7.42-7.49 (m, 2H, Ar), 7.69 (d, *J* = 7.2 Hz, 1H, Ar), 7.91 (t, *J* = 8.2 Hz, 1H, Ar), 8.03-8.08 (m, 2H, Ar), 8.54 (d, *J* = 8.3 Hz, 1H, Ar), 10.41 (s, 1H, NH), 11.15 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 22.10, 30.98, 49.29, 115.96 (d, *J*_{C,F} = 22 Hz); 118.03, 118.67, 128.09 (d, *J*_{C,F} = 235 Hz), 130.12, 131.49, 136.18, 136.75, 162.70, 164.08, 166.56,
- 35

168.22, 169.29, 172.27; Anal Calcd for $C_{20}H_{14}N_3O_5F + 0.2 H_2O$: C, 60.21; H, 3.64; N, 10.53; F, 4.76; H_2O , 0.90. Found: C, 60.17; H, 3.55; N, 10.47; F, 4.90; H_2O , 0.95.

5 **N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-trifluoromethyl-benzamide I-66**

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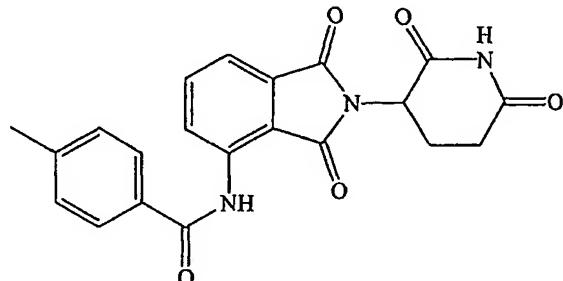
- 15 A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (0.6 g, 2.2 mmol) and 4-(trifluoromethyl)benzoyl chloride (1 g, 4.8 mmol) in THF (20 mL) was heated to reflux for 15 h. The solvent was removed *in vacuo* to give a solid. The solid was slurried in methanol (20 mL) for 2h. The suspension was filtered and washed with ether (15 mL) then methanol (15 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-trifluoromethyl-benzamide as a white solid (750 mg, 77 % yield): mp, 213-215 °C; 1H NMR (DMSO-d6) δ 2.05-2.10 (m, 1H, CHH), 2.49-2.65 (m, 2H, CH_2), 2.83-2.98 (m, 1H, CHH), 5.18 (dd, $J = 5.2, 12.5$ Hz, 1H, NCH), 7.72 (d, $J = 7.2$ Hz, 1H, Ar), 7.90-8.02 (m, 3H, Ar), 8.16-8.19 (m, 2H, Ar), 8.49 (d, $J = 8.4$ Hz, 1H, Ar), 10.58 (s, 1H, NH), 11.17 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 21.99, 30.92, 48.99, 118.88, 119.36, 119.32, 123.76 (q, $J_{C-F} = 271$ Hz); 125.99 (q, $J_{C-F} = 3.6$ Hz), 127.10 128.37, 131.54, 132.16 (q, $J_{C-F} = 32$ Hz), 136.00, 136.26, 13721, 164.05, 166.59, 167.65, 169.68, 172.73; Anal Calcd for $C_{21}H_{14}N_3O_5F_3$: C, 56.64; H, 3.17; N, 9.44; F, 12.80. Found: C, 56.25; H, 3.05; N, 9.32; F, 12.69.

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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methyl-benzamide I-67

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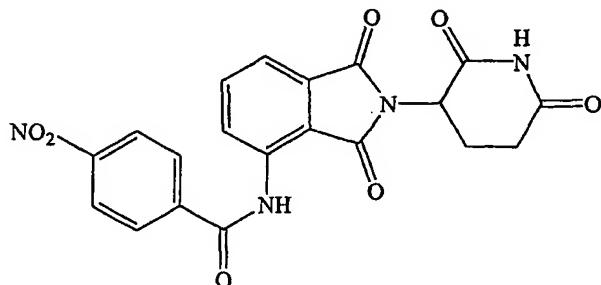


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A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and 4-methylbenzoyl chloride (1.1 g, 8.0 mmol) in THF (40 mL) was heated to reflux for 36 h. To the mixture was added methanol (5 mL) to give a suspension. The 15 suspension was filtered and washed with methanol (15 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methyl-benzamide as a yellow solid (1.3 g, 83 % yield): mp, 322-324 °C; ¹H NMR (DMSO-d₆) δ 2.06-2.10 (m, 1H, CHH), 2.41 (s, 3H, CH₃), 2.50-2.65 (m, 2H, CH₂), 2.83-2.97 (m, 1H, CHH), 5.19 (dd, *J*=5.3, 12.6 Hz, 1H, NCH), 7.42 (d, *J*=8.1 Hz, 2H, Ar), 7.67 (d, *J*=7.2 Hz, 1H, Ar), 7.86-20 7.93 (m, 3H, Ar), 8.62 (d, *J*=8.4 Hz, 1H, Ar), 10.37 (s, 1H, NH), 11.18 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 21.07, 21.99, 30.93, 48.99, 117.57, 118.58, 125.94, 127.28, 129.58, 130.44, 131.33, 136.34, 136.77, 142.96, 164.80, 166.65, 168.29, 169.69, 172.72; Anal Calcd for C₂₁H₁₇N₃O₅: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.65; H, 4.17; N, 10.70.

25 N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-nitro-benzamide I-68

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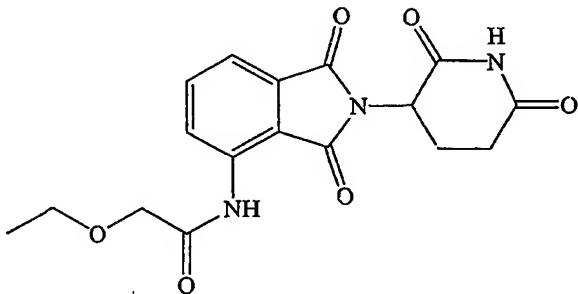


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A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (2.2 g, 8.0 mmol) and 4-nitrobenzoyl chloride (3.0 g, 16.0 mmol) in THF (80 mL) was heated to reflux for 15 h. To the mixture was added methanol (20 mL) to give a suspension. The suspension was filtered and washed with methanol (20 mL) to give N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-nitro-benzamide as a white solid (2.5 g, 73 % yield): mp, 298-300 °C; ¹H NMR (DMSO-d₆) δ 2.06-2.10 (m, 1H, CHH), 2.49-2.65 (m, 2H, CH₂), 2.83-2.98 (m, 1H, CHH), 5.18 (dd, *J* = 5.2, 12.6 Hz, 1H, NCH), 7.73 (d, *J* = 7.2 Hz, 1H, Ar), 7.93 (t, *J* = 8.0 Hz, 1H, Ar), 8.19-8.22 (m, 2H, Ar), 8.42-8.47 (m, 3H, Ar), 10.65 (s, 1H, NH), 11.18 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 21.99, 30.92, 48.99, 119.30, 119.56, 124.06, 127.49, 129.01, 131.58, 135.77, 136.23, 138.96, 149.69, 163.65, 166.57, 167.48, 169.68, 172.72; Anal Calcd for C₂₀H₁₄N₄O₇: C, 56.88; H, 3.34; N, 13.27. Found: C, 57.15; H, 3.02; N, 13.22.

N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-ethoxy-acetamide I-69

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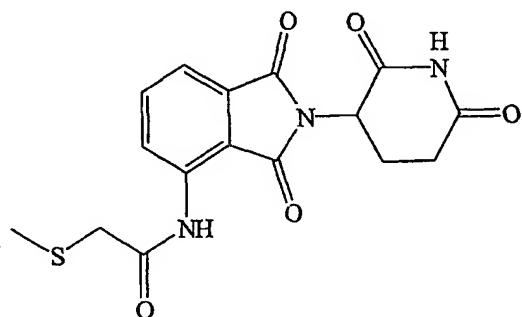


To a solution of ethoxyacetic acid (0.8 mL, 8.5 mmol) and oxalyl chloride (0.7 mL, 8.0 mmol) in ether (5 mL) was added DMF (0.03 mL) at room temperature. After 3h, 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and THF (40 mL) was added to the mixture. Then the mixture was heated to reflux for 15 h. To the mixture was added methanol (10 mL) to give a suspension. The suspension was filtered and washed with methanol (10 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-ethoxy-acetamide as a white solid (1.3 g, 87 % yield): mp, 253-255 °C; ¹H NMR (DMSO-d₆) δ 1.27 (t, *J* = 7.0 Hz, 3H, CH₃), 2.06-2.10 (m, 1H, CHH), 2.46-2.64 (m, 2H, CH₂), 2.84-2.98 (m, 1H, CHH), 3.66 (q, *J* = 7.0 Hz, 2H, CH₂), 4.14 (s, 2H, CH₂), 5.17 (dd, *J* = 5.2, 12.7 Hz, 1H, NCH), 7.62 (d, *J* = 7.2 Hz, 1H, Ar), 7.87 (t, *J* = 8.2 Hz, 1H, Ar), 8.75 (d, *J* = 8.4 Hz, 1H, Ar), 10.39 (s, 1H, NH), 11.16 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.88, 21.93, 30.92, 48.98, 66.89, 69.49, 116.00, 118.28, 124.25, 131.31, 135.99,

136.53, 166.69, 168.31, 169.49, 169.73, 174.71; Anal Calcd for C₁₇H₁₇N₃O₆: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.82; H, 4.71; N, 11.60.

N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methoxy-
 5 benzamide I-70

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15 To a solution of (methylthio)acetic acid (0.77 mL, 8.9 mmol) and oxalyl chloride (0.7 mL, 8.0 mmol) in ether (5 mL) was added DMF (0.02 mL) at room temperature. After 3h, 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and THF (40 mL) was added to the mixture. Then the mixture was heated to reflux for 15 h. To the mixture was added methanol (10 mL) to give a suspension. The suspension was filtered and
 20 washed with methanol (10 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylsulfanyl-acetamide as a white solid (1.0 g, 69 % yield): mp, 228-230 °C; ¹H NMR (DMSO-d6) δ 2.05-2.10 (m, 1H, CHH), 2.18 (s, 3H, CH₃), 2.46-2.65 (m, 2H, CH₂), 2.82-2.95 (m, 1H, CHH), 3.53 (s, 2H, CH₂), 5.17 (dd, J = 5.2, 12.6 Hz, 1H, NCH), 7.63 (d, J = 7.2 Hz, 1H, Ar), 7.86 (t, J = 7.5 Hz, 1H, Ar), 8.61 (d, J = 8.4 Hz, 1H, Ar), 10.39 (s, 1H, NH), 11.16 (s, 1H, NH); ¹³C NMR (DMSO-d6) δ 15.62, 21.96, 30.93, 37.99, 48.94, 116.69, 118.46, 125.28, 131.44, 136.31, 166.67, 167.88, 168.63, 169.78, 172.75; Anal Calcd for C₁₆H₁₅N₃O₅S: C, 53.18; H, 4.18; N, 11.63. Found: C, 53.26; H, 4.17; N, 11.52.

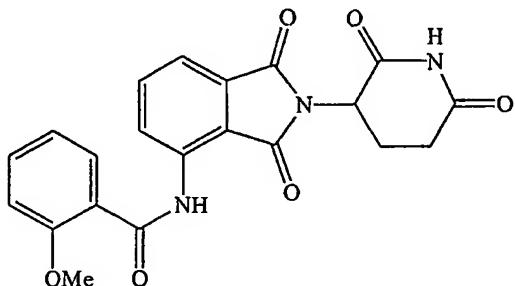
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methoxy-benzamide I-71

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A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (660 mg, 2.4 mmol) and 2-methoxybenzoyl chloride (0.7 mL, 4.7 mmol) in THF (20 mL) was heated to
 15 reflux for 15 h. To the mixture was added methanol (5 mL) to give a suspension. The suspension was filtered and washed with methanol (20 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methoxy-benzamide as a white solid (760 mg, 78 % yield): mp, 286-287 °C; ¹H NMR (DMSO-d₆) (at 340K) δ 2.09-2.14 (m, 1H, CHH), 2.55-2.66 (m, 2H, CH₂), 2.85-2.98 (m, 1H, CHH), 4.14 (s, 3H, OCH₃), 5.19 (dd, J = 5.5, 12.9 Hz, 1H, NCH), 7.17 (t, J = 7.2 Hz, 1H, Ar), 7.30 (d, J = 8.3 Hz, 1H, Ar), 7.61-7.68 (m, 2H, Ar), 7.89 (t, J = 7.7 Hz, 1H, Ar), 8.12 (dd, J = 1.8, 7.9 Hz, 1H Ar), 9.03 (d, J = 8.5 Hz, 1H, Ar), 11.17 (s, 1H, NH), 11.64 (s, 1H, NH); ¹³C NMR (DMSO-d₆) (at 340K) δ 22.09, 31.02, 49.29, 56.19, 112.65, 116.31, 117.93, 120.66, 121.14, 125.52, 131.59, 131.75, 134.34, 136.22, 137.00, 157.64, 163.82, 166.69, 168.15, 169.43, 172.32;
 20 Anal Calcd for C₂₁H₁₇N₃O₆: C, 61.92; H, 4.21; N, 10.31. Found: C, 62.05; H, 4.10; N,
 25 10.38.

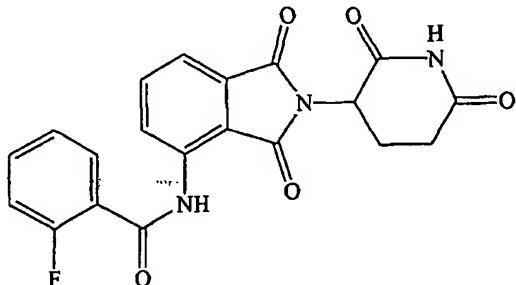
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N-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-fluoro-benzamide I-72

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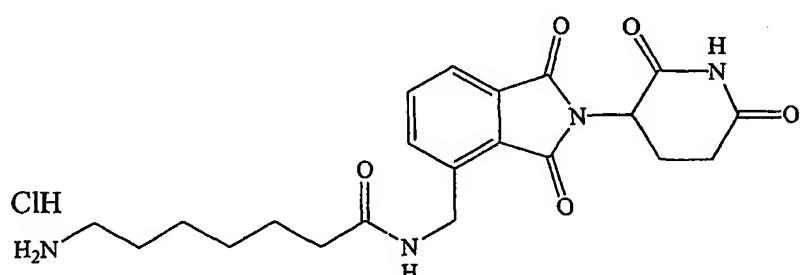
A mixture of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.1 g, 4.0 mmol) and 2-fluorobenzoyl chloride (1.0 mL, 8.4 mmol) in THF (40 mL) was heated to reflux for 15 h. To the mixture was added methanol (10 mL) to give a suspension. The 15 suspension was filtered and washed with methanol (20 mL) to give N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-fluoro-benzamide as a white solid (1.5 g, 93 % yield): mp, 300-302 °C; ¹H NMR (DMSO-d6) δ 2.05-2.12 (m, 1H, CHH), 2.45-2.65 (m, 2H, CH₂), 2.83-2.97 (m, 1H, CHH), 5.18 (dd, *J* = 5.5, 12.9 Hz, 1H, NCH), 7.40-7.49 (m, 2H, Ar), 7.67-7.76 (m, 2H, Ar), 7.88-7.98 (m, 1H, Ar), 8.01-8.05 (m, 1H, Ar), 8.76 (d, *J* = 8.4 Hz, 1H Ar), 10.56 (d, *J*_{N,F} = 10 Hz, 1H, NH), 11.17 (s, 1H, NH); ¹³C NMR (DMSO-d6) δ 21.96, 30.92, 48.97, 116.48, 116.97 (d, *J*_{C,F} = 14 Hz), 118.82, 120.87 (d, *J*_{C,F} = 12 Hz), 125.32 (d, *J*_{C,F} = 1.5 Hz), 125.74, 131.32, 131.39, 134.88 (d, *J*_{C,F} = 9 Hz), 136.22, 136.48, 159.75 (d, *J*_{C,F} = 252 Hz), 161.76 (d, *J*_{C,F} = 7 Hz), 166.58, 168.04, 169.70, 172.71; Anal Calcd for C₂₀H₁₄N₃O₅F: C, 60.76; H, 3.57; N, 10.63; F, 4.81. Found: 20 C, 60.70; H, 3.64; N, 10.64; F, 4.91.

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7-Amino-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisoindolin-4-yl]methyl}heptanamide Hydrochloride I-73}

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Step 1: 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.7g, 4.62 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, 1-

- 5 hydroxybenzotriazole (0.3g, 2.22 mmol), N-BOC-7-aminoheptanonic acid (0.54g, 2.22 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.53g, 2.78 mmol) were added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N citric acid (30 mL), H₂O (2x30 mL), brine (30 mL) and dried 10 (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1:1) to give 7-[(tert-butoxy)carbonylamino]-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}heptanamide (0.74g, 77%) as a white solid: ¹H NMR (CDCl₃) δ 11.4 (s, 1H), 8.44 (t, J=5.7 Hz, 1H), 7.83-7.78 (m, 2H), 7.68-7.65 (m, 1H), 6.77 (t, J=5.1 Hz, 1H), 5.19-5.11 (dd, J=5.4 and 12.4 Hz, 1H), 4.71 (d, J=5.8 Hz, 2H), 2.93-2.84 (m, 3H), 2.63-2.49 (m, 2H), 2.21-2.05 (m, 1H), 1.55-1.49 (m, 2H), 15 1.36 (s, 9H), 1.36-1.20 (m, 6H).

Step 2: A 4N HCl solution in dioxane (1.5 mL) was added to a stirred solution of 7-[(tert-butoxy)carbonylamino]-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-

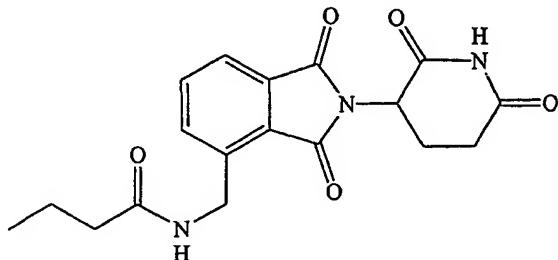
- 20 yl]methyl}heptanamide (0.72g, 1.40 mmol) in CH₂Cl₂ (25 mL) and stirred for 17 hours. The resulting suspension was filtered to give 7-amino-N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}heptanamide hydrochloride (0.26g, 41%) as a white solid: mp 187-189°C; ¹H NMR (DMSO-d₆) δ 11.12 (s, 1H), 8.52 (t, J=5.7 Hz, 1H), 7.93 (b, 3H), 7.88-7.67 (m, 3H), 5.18-5.11 (dd, J=5.3 and 12.4 Hz, 1H), 4.72 (d, J=5.7 Hz, 2H), 2.91-2.50 25 (m, 5H), 2.21 (t, J=7.2 Hz, 2H), 2.08-2.04 (m, 1H), 1.57-1.52 (m, 4H), 1.31-1.29 (m, 4H); ¹³C NMR (CDCl₃) δ 172.70, 172.55, 169.77, 167.44, 166.90, 139.54, 134.68, 133.08, 131.47, 127.01, 121.77, 48.82, 38.64, 37.53, 35.00, 30.90, 28.05, 26.73, 25.50, 24.89, 21.95; Anal. Calcd. For C₂₁H₂₇N₄O₅Cl + 0.64 H₂O: C, 54.95; H, 6.13; N, 12.21; Cl, 7.72. Found: C, 54.56; H, 6.10; N, 11.96; Cl, 8.04.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}butanamide I-74}

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10 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, butyryl chloride (0.24g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and residue was purified by chromatography (SiO₂, CH₂Cl₂:EtOAc 1:1) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}butanamide (0.41g, 62%) as a white solid: mp 121-123 °C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 8.44 (t, J=5.55 Hz, 1H), 7.87-7.66 (m, 3H), 5.19-5.12 (dd, J=5.1 and 12.4 Hz, 1H), 4.72 (d, J=5.6 Hz, 2H), 2.96-2.85 (m, 1H), 2.63-2.51 (m, 2H), 2.17 (t, J=7.2 Hz, 2H), 2.08-2.04 (m, 1H), 1.63-1.51 (m, 2H), 0.87 (t, J=7.3 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.71, 172.47, 169.77, 167.46, 166.92, 139.53, 134.68, 133.11, 131.49, 127.04, 121.77, 48.84, 37.55, 37.16, 30.91, 21.96, 18.60, 13.63; Anal. Calcd. For C₁₈H₁₉N₃O₅: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.46; H, 5.36; N, 11.59.

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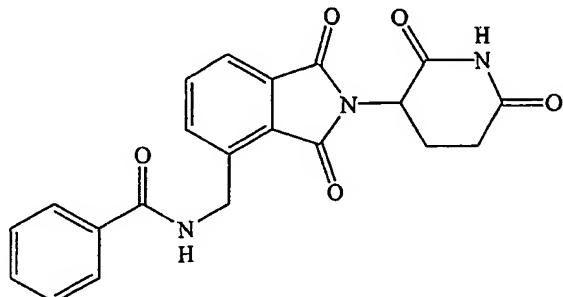
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}benzamide I-75}

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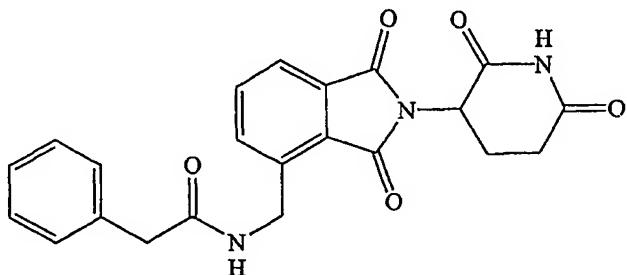
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, benzoyl chloride (0.31g, 2.22 mmol) was added. The mixture was stirred at room temperature for 15 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed and the residue was purified by chromatography (SiO₂, CH₂Cl₂; EtOAC 6:4) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}benzamide (0.55g, 76%) as a white solid: mp 227-229°C; ¹H NMR (DMSO-d₆) δ 11.16 (s, 1H), 9.16 (t, J=5.7 Hz, 1H), 7.95-7.72 (m, 5H), 7.60-7.46 (m, 3H), 5.22-5.12 (dd, J=5.4 and 12.8 Hz, 1H), 4.96 (d, J=5.7 Hz, 2H), 2.98-2.85 (m, 1H), 2.65-2.50 (m, 2H), 2.11-2.06 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.72, 169.80, 167.54, 166.96, 166.60, 139.34, 134.77, 133.92, 133.02, 131.52, 131.42, 128.34, 127.28, 127.12, 121.83, 48.88, 38.32, 30.93, 21.98; Anal. Calcd. For C₂₁H₁₇N₃O₅: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.47; H, 4.50; N, 10.34.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}phenylacetamide I-76}

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.65g, 4.26mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, phenylacetyl chloride (0.35g, 2.22mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 6:4) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2-phenylacetamide (0.41g, 55%) as a white solid: mp 128-130°C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 8.67 (t, J=5.5 Hz, 1H), 7.80-7.61 (m, 3H), 7.29 (s, 5H), 5.19-5.12 (dd, J=5.1 and 12.4 Hz, 1H), 4.71 (d, J=5.5 Hz, 2H), 3.53 (s, 2H), 2.96-2.83 (m, 1H), 2.63-2.50 (m, 2H), 2.08-2.03 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.77, 170.65, 169.82, 167.45, 166.93, 139.19, 136.15, 134.68, 133.18, 131.53, 129.05, 128.25, 127.13, 126.43, 121.90, 48.85, 42.24, 37.85, 30.93, 21.98; Anal. Calcd. For C₂₂H₁₉N₃O₅: C, 65.18; H, 4.72; N, 10.36. Found: C, 65.16; H, 4.75; N, 10.11.

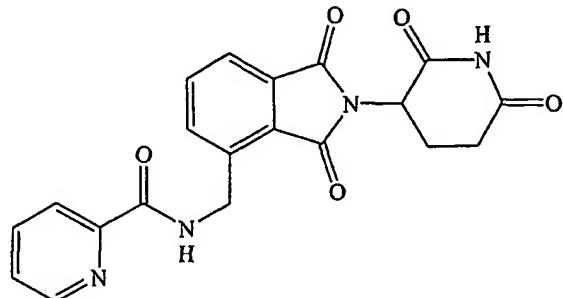
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2pyridylcarboxamide I-77}

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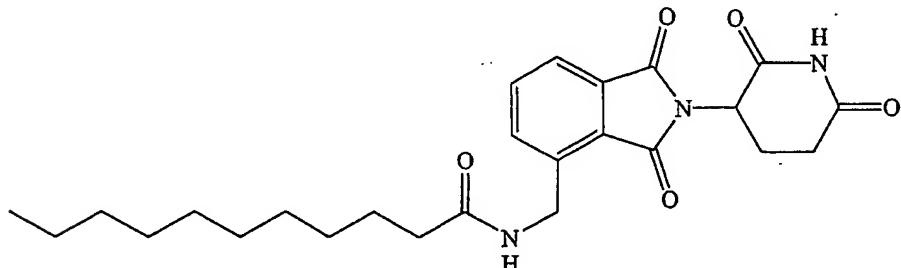
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.98g, 6.48mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, picolinoyl chloride hydrochloride (0.41g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCL (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃OH 97.5:2.5) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2-pyridylcarboxamide (0.40g, 55%) as a white solid: mp 155-157°C; ¹H NMR (DMSO-d₆) δ 11.15 (s, 1H), 9.50 (t, J=6.2 Hz, 1H), 8.70 (d, J=4.6 Hz, 1H), 8.08-7.98 (m, 2H), 7.82-7.62 (m, 4H), 5.21-5.14 (dd, J=5.4 and 12.6 Hz, 1H), 4.97 (d, J=6.3 Hz, 2H), 2.99-2.84 (m, 1H), 2.65-2.50 (m, 2H), 2.10-2.06 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.77, 169.85, 167.59, 166.99, 164.38, 149.59, 148.56, 139.02, 137.87, 134.79, 132.95, 131.57, 127.16, 126.76, 122.05, 121.87, 48.87, 38.37, 30.94, 21.97; Anal. Calcd. For C₂₀H₁₆N₄O₅+0.08H₂O: C, 61.08; H, 4.13; N, 14.25. Found: C, 61.48; H, 4.22; N, 13.87.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}undecamide I-78}

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60 g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, undecanoyl chloride (0.45g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 6:4) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}undecanamide (0.53g, 63%) as a white solid:

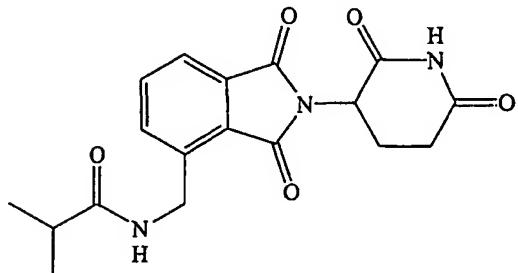
mp 138-139 °C; ¹H NMR (DMSO-d₆) δ 11.12 (s, 1H), 8.42 (t, J=5.9 Hz, 1H), 7.85-7.78 (m, 2H), 7.71-7.65 (m, 1H), 5.18-5.11 (dd, J=5.4 and 12.5 Hz, 1H), 4.72 (d, J=5.9 Hz, 2H), 2.96-2.83 (m, 1H), 2.64-2.47 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.08-2.04 (m, 1H), 1.55-1.50 (m, 2H), 1.24 (s, 14H), 0.85 (t, J=6.1 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.74, 172.63, 169.80, 167.47, 166.93, 139.55, 134.65, 133.10, 131.50, 127.04, 121.79, 48.83, 37.55, 35.21, 31.28, 30.92, 28.94, 28.74, 28.67, 25.20, 22.08, 21.97, 13.94; Anal. Calcd. For C₂₅H₃₃N₃O₅: C, 65.91; H, 7.30; N, 9.23. Found: C, 66.08; H, 7.13; N, 9.23.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2methylpropanamide I-79}

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60g, 1.85 mmol) in CH_3CN (50 mL). After stirring for 20 min, isobutyryl chloride (0.24g, 2.22 mmol) was added. The mixture was stirred at room temperature for 15 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (70 mL). The CH_2Cl_2 solution was washed with 1N HCl (30 mL), H_2O (30 mL), brine (30 mL) and dried (MgSO_4). The solvent was removed *in vacuo* and the solid was purified from ether (10 mL) and hexane (10 mL) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}2-methylpropanamide (0.48g, 73%) as a white solid: mp 218-220°C; ^1H NMR (DMSO-d_6) δ 11.13 (s, 1H), 8.39 (t, $J=5.8$ Hz, 1H), 7.87-7.78 (m, 2H), 7.66-7.63 (m, 1H), 5.19-5.12 (dd, $J=6.9$ and 12.5 Hz, 1H), 4.71 (d, $J=5.8$ Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.43 (m, 3H), 2.08-2.04 (m, 1H), 1.07 (d, $J=6.9$ Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 176.52, 172.75, 169.82, 167.49, 166.95, 139.54, 134.77, 132.85, 131.50, 127.02, 121.77, 48.83, 37.48, 33.98, 30.92, 21.96, 19.53; Anal. Calcd. For $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.48; H, 5.33; N, 11.64.

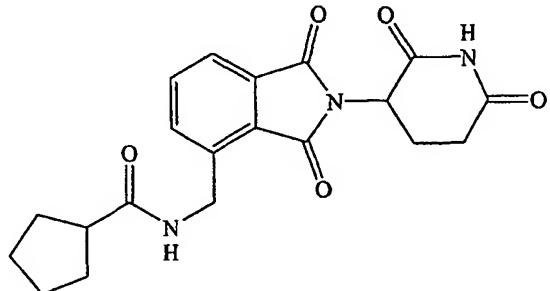
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclopentylcarboxamide
I-80

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, 15 cyclopentanecarbonyl chloride (0.29g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the solid was stirred with ether (20 mL) to give N- {[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclopentylcarboxamide (0.59g, 83%) as a white solid: mp 175-177°C; ¹H NMR (DMSO-d₆) δ 11.13 (s, 1H), 8.41 (t, J=5.7 Hz, 1H), 7.87-7.78 (m, 2H), 7.66-7.63 (m, 1H), 5.19-5.12 (dd, J=5.3 and 12.5 Hz, 1H), 4.72 (d, J=5.8 Hz, 2H), 2.98-2.83 (m, 1H), 2.73-2.51 (m, 3H), 2.08-2.04 (m, 1H), 1.81-1.51 (m, 8H); ¹³C NMR (DMSO-d₆) δ 175.71, 172.75, 169.82, 167.49, 166.95, 139.68, 134.76, 132.91, 131.50, 127.01, 121.77, 48.84, 44.20, 37.60, 30.93, 29.96, 25.60, 21.97; Anal. Calcd. For C₂₀H₂₁N₃O₅: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.52; H, 5.55; N, 10.81.

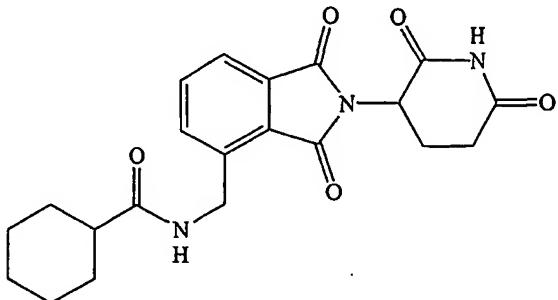
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclohexylcarboxamide}
I-81

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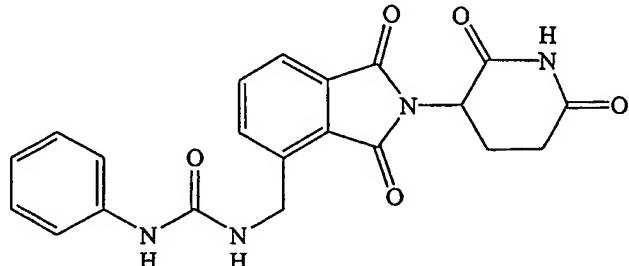
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.62g, 4.08 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.60g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min,
 15 cyclohexanecarbonyl chloride (0.33g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCL (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 6:4) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclohexylcarboxamide (0.53g, 72%) as a white solid: mp 142-144°C; ¹H NMR (DMSO-d₆) δ 11.13 (s, 1H), 8.36 (t, J=5.8 Hz, 1H), 7.86-7.77 (m, 2H), 7.64-7.61 (m, 1H), 5.18-5.11 (dd, J=5.3 and 12.5 Hz, 1H), 4.70 (d, J=5.8 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.47 (m, 2H), 2.26-2.17 (m, 1H), 2.08-2.03 (m, 1H), 1.79-1.61 (m, 5H), 1.43-1.12 (m, 5H); ¹³C NMR (DMSO-d₆) δ 175.58, 172.75, 169.82, 167.49, 166.96, 139.68, 134.75, 132.76, 131.49, 126.99, 121.73, 48.83, 43.90, 37.43, 30.92, 29.20, 25.43, 25.24, 21.96; Anal. Calcd. For C₂₁H₂₃N₃O₅: C, 63.47; H, 5.83; N, 10.57. Found: C, 63.12; H, 5.68; N, 10.41.

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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}-(phenylamino)-carboxamide I-82

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- 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g. 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, phenyl isocyanate (0.33g, 2.77 mmol) was added. The mixture was stirred at room temperature for 15 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂ : EtOAc 7:3) to give N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl]-(phenylamino)carboxamide (0.23g, 31%) as a white solid: mp 20 212-214°C; ¹H NMR (DMSO-d₆) δ 11.15 (s, 1H), 8.78 (s, 1H), 7.88-7.76 (m, 3H), 7.37 (d, J=7.7 Hz, 2H), 7.21 (t, J=7.7 Hz, 2H), 6.89 (t, J=7.3 Hz, 1H), 6.76 (t, J=5.9 Hz, 1H), 5.20-5.13 (dd, J=5.3 and 12.5 Hz, 1H), 4.72 (d, J=5.9 Hz, 2H), 2.97-2.84 (m, 1H), 2.65-2.49 (m, 2H), 2.09-2.05 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.72, 169.79, 167.58, 166.99, 155.22, 140.25, 134.69, 133.63, 131.59, 128.60, 127.18, 121.83, 121.18, 117.70, 48.86, 38.71, 30.92, 21.97; Anal. Calcd. For C₂₁H₁₈N₄O₅: C, 62.07; H, 4.46; N, 13.79. Found: C, 62.14; H, 4.49; N, 13.49.

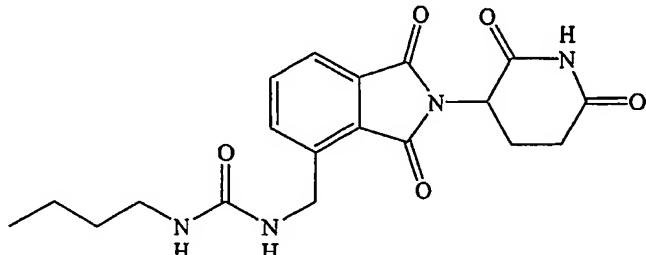
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(butylamino)carboxamide
I-83

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, n-butyl 15 isocyanate (0.27g, 2.77 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1:1) to give N-{[2-(2,6-dioxo(3-piperidyl))1,3- 20 dioxoisooindolin-4-yl]methyl}(butylamino)carboxamide (0.44g, 61%) as a white solid: mp 172-174°C; ¹H NMR (DMSO-d₆) δ 11.13 (s, 1H), 7.86-7.68 (m, 3H), 6.42 (t, J=5.9 Hz, 1H), 6.12 (t, J=5.4 Hz, 1H), 5.18-5.11 (dd, J=5.2 and 12.4 Hz, 1H), 4.63 (d, J=5.9 Hz, 1H), 3.03-2.83 (m, 3H), 2.64-2.51 (m, 2H), 2.08-2.04 (m, 1H), 1.37-1.22 (m, 4H), 0.86 (t, J=7.0 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.70, 169.77, 167.54, 167.00, 157.98, 141.14, 134.56, 25 133.33, 131.47, 126.94, 121.58, 48.80, 38.98, 38.70, 32.01, 30.90, 21.95, 19.46, 13.64; Anal. Calcd. For C₁₉H₂₂N₄O₅: C, 59.06; H, 5.74; N, 14.50. Found: C, 59.24; H, 5.53; N, 14.37.

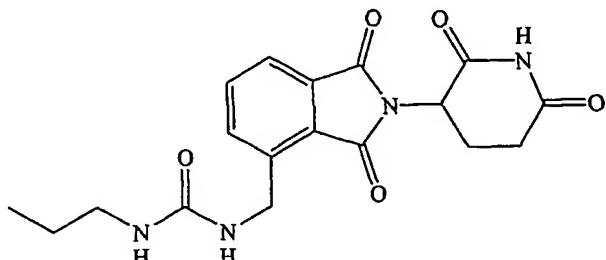
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(propylamino)-carboxamide I-84}

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, propyl 15 isocyanate (0.24 g, 2.77 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃OH 100: 3) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(propylamino)carboxamide (0.13g, 20%) as a white solid: mp160-162 °C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.86-7.69 (m, 3H), 6.44 (t, J=5.9 Hz, 1H), 6.16 (t, J=1H), 5.18-5.11 (dd, J=5.3 and 12.4 Hz, 1H), 4.63 (d, J=5.9 Hz, 2H), 2.99-2.83 (m, 3H), 2.64-2.50 (m, 2H), 2.08-2.04 (m, 1H), 1.42-1.32 (m, 2H), 0.83 (t, J=7.3 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.78, 169.84, 167.59, 167.05, 158.03, 141.16, 134.62, 25 133.34, 131.51, 126.96, 121.63, 48.82, 41.18, 30.94, 23.15, 21.99, 11.33; Anal. Calcd. For C₁₈H₂₀N₄O₅: C, 58.06; H, 5.41; N, 15.05. Found: C, 57.94; H, 5.31; N, 14.90.

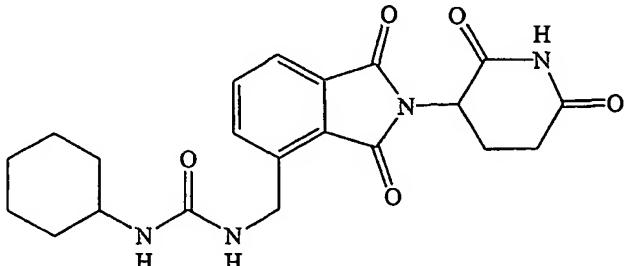
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclohexylamino)-carboxamide I-85

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, cyclohexyl isocyanate (0.35g, 2.77 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: EtOAc 1:1) to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclohexylamino)carboxamide (0.37g, 49%) as a white solid: mp 208-210°C; ¹H NMR (DMSO-d₆) δ 11.13 (s, 1H), 7.86-7.68 (m, 3H), 6.34 (t, J=5.8Hz, 1H), 6.04 (d, J=7.9 Hz, 1H), 5.18-5.11 (dd, J=5.3 and 12.4 Hz, 1H), 4.62 (d, J=5.8 Hz, 2H), 3.37 (m, 1H), 2.96-2.83 (m, 1H), 2.63-2.50 (m, 2H), 2.08-2.04 (m, 1H), 1.76-1.02 (m, 10H); ¹³C NMR (DMSO-d₆) δ 172.78, 169.84, 167.59, 167.04, 157.28, 141.13, 134.64, 133.42, 131.51, 126.98, 121.64, 48.82, 47.91, 38.66, 33.23, 30.94, 25.27, 24.47, 21.99; Anal. Calcd. For C₂₁H₂₄N₄O₅: C, 61.16; H, 5.87; N, 13.58. Found: C, 61.21; H, 5.79; N, 13.63.

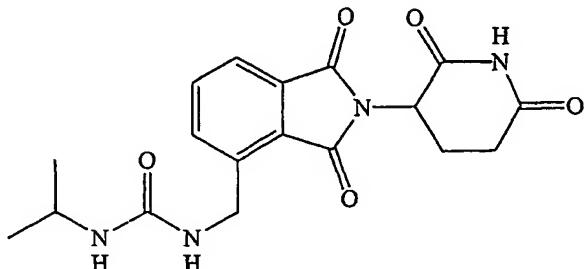
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N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}{[(methylethylamino)]-}carboxamide I-86}

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- 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, isopropyl 15 isocyanate (0.24g, 2.77 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃OH 97.5:2.5) to give N-{{[2-(2,6-dioxo(3-piperidyl))-}16 20 1,3-dioxoisooindolin-4-yl]methyl}{[(methylethylamino)]carboxamide (0.25g, 36%) as a white solid: mp 180-182°C; ¹H NMR (DMSO-d₆) δ 11.19 (s, 1H), 7.87-7.68 (m, 3H), 6.33 (t, J=5.9 Hz, 1H), 6.02 (d, J=7.5 Hz, 1H), 5.18-5.11 (dd, J=5.2 and 12.4 Hz, 1H), 4.62 (d, J=5.9 Hz, 2H), 3.73-3.35 (m, 1H), 2.98-2.83 (m, 1H), 2.63-2.50 (m, 2H), 2.08-2.04 (m, 1H), 1.04 (d, J=6.5 Hz, 6H); ¹³C NMR (DMSO-d₆) δ 172.78, 169.85, 167.59, 167.05, 157.36, 141.16, 134.65, 133.39, 131.52, 126.98, 121.64, 48.82, 41.03, 38.64, 30.94, 23.18, 21.99; Anal. Calcd. For C₁₈H₂₀N₄O₅: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.20; H, 5.44; N, 14.95.

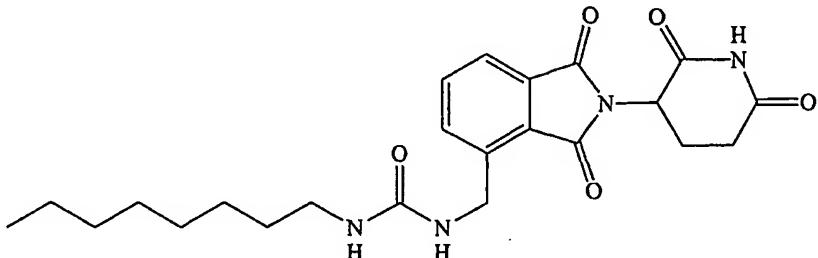
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(octylamino)carboxamide
I-87

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1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, octyl 15 isocyanate (0.44g, 2.77 mmol) was added. The mixture was stirred at room temperature for 17 hours. The slurry mixture was filtered and the solid was recrystallized from methanol to give N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(octylamino)carboxamide (0.46g, 56%) as a white solid: mp 160-162 °C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.85-7.68 (m, 3H), 6.43 (t, J=6.0 Hz, 1H), 6.13 (t, J=5.6 Hz, 1H), 5.18-5.11 (dd, J=5.3 and 12.5 Hz, 1H), 4.62 (d, J=6.0 Hz, 2H), 3.02-2.83 (m, 3H), 2.64-2.50 (m, 2H), 2.08-2.04 (m, 1H), 1.36-1.24 (m 12H), 0.85 (t, J=6.2 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.75, 169.82, 167.57, 167.03, 157.99, 141.19, 134.57, 133.33, 131.50, 126.95, 121.61, 48.82, 39.32, 38.83, 31.21, 30.93, 29.92, 28.73, 28.69, 26.37, 22.07, 21.98, 13.93; Anal. Calcd. For C₂₃H₃₀N₄O₅: C, 62.43; H, 6.83; N, 12.66. Found: C, 62.27; H, 6.94; N, 12.54.

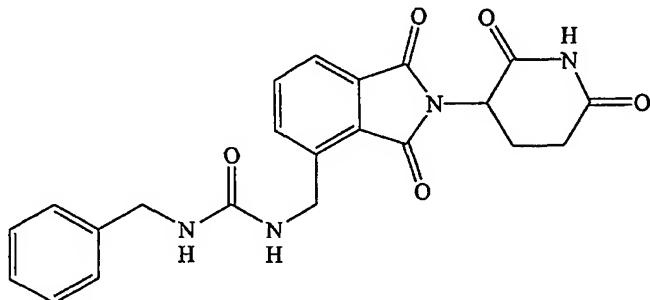
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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(benzylamino)-carboxamide I-88

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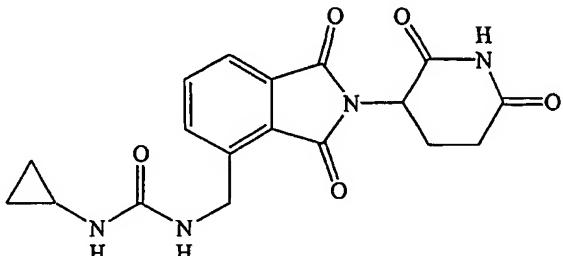
- 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, benzyl isocyanate (0.32g, 2.41 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 1N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO₂, CH₂Cl₂: CH₃OH 96:4) to give N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl](benzylamino)carboxamide (0.42g, 54%) as a white solid: mp 192-194°C; ¹H NMR (DMSO-d₆) δ 11.13 (s, 1H), 7.86-7.69 (m, 3H), 7.34-7.19 (m, 5H), 6.67 (t, J=5.8 Hz, 1H), 6.60 (t, J=5.9 Hz, 1H) 5.18-5.11 (dd, J= 5.3 and 12.5 Hz, 1H), 4.67 (d, J=5.9 Hz, 2H), 4.23 (d, J=5.8 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.50 (m, 2H), 2.07-2.03 (m, 1H); ¹³C NMR (DMSO-d₆) δ 175.63, 172.75, 167.56, 167.03, 158.05, 141.01, 140.70, 134.61, 133.31, 131.52, 128.19, 126.98, 126.55, 121.66, 48.83, 42.99, 30.93, 21.98; Anal. Calcd. For C₂₂H₂₀N₄O₅: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.78; H, 4.53; N, 13.18.

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N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}(cyclopropylamino)-carboxamide I-89

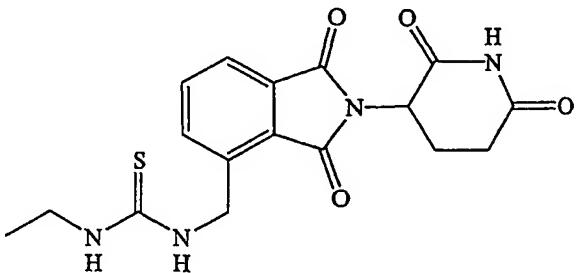
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- 10 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.58g, 3.81mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, 4-nitrophenyl-N-cyclopropylcarbamate (0.41g, 1.85 mmol) was added. The mixture was stirred at room temperature for 17 hours. The mixture was filtered and the solid was recrystallized from methanol to give N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl](cyclopropylamino)carboxamide (0.53g, 77%) as a white solid: mp 245-247°C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.87-7.69 (m, 3H), 6.58 (t, J=5.7 Hz, 1H), 6.45 (d, J=2.2 Hz, 1H) 5.19-5.11 (dd, J=5.4 and 12.5 Hz, 1H), 4.65 (d, J=6.1 Hz, 2H), 2.96-2.83 (m, 1H), 2.64-2.40 (m, 3H), 2.08-2.04 (m, 1H), 0.62-0.55 (m, 2H), 0.40-0.34 (m, 2H); ¹³C NMR (DMSO-d₆) δ 172.75, 169.82, 167.63, 167.04, 158.69, 141.11, 134.61, 133.26, 131.49, 126.94, 121.60, 48.83, 30.93, 22.37, 21.97, 6.59; Anal. Calcd. For C₁₈H₁₈N₄O₅: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.26; H, 4.82; N, 14.85.
- 15 recrystallized from methanol to give N-[(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl](cyclopropylamino)carboxamide (0.53g, 77%) as a white solid: mp 245-247°C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.87-7.69 (m, 3H), 6.58 (t, J=5.7 Hz, 1H), 6.45 (d, J=2.2 Hz, 1H) 5.19-5.11 (dd, J=5.4 and 12.5 Hz, 1H), 4.65 (d, J=6.1 Hz, 2H), 2.96-2.83 (m, 1H), 2.64-2.40 (m, 3H), 2.08-2.04 (m, 1H), 0.62-0.55 (m, 2H), 0.40-0.34 (m, 2H); ¹³C NMR (DMSO-d₆) δ 172.75, 169.82, 167.63, 167.04, 158.69, 141.11, 134.61, 133.26, 131.49, 126.94, 121.60, 48.83, 30.93, 22.37, 21.97, 6.59; Anal. Calcd. For C₁₈H₁₈N₄O₅: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.26; H, 4.82; N, 14.85.
- 20 (DMSO-d₆) δ 172.75, 169.82, 167.63, 167.04, 158.69, 141.11, 134.61, 133.26, 131.49, 126.94, 121.60, 48.83, 30.93, 22.37, 21.97, 6.59; Anal. Calcd. For C₁₈H₁₈N₄O₅: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.26; H, 4.82; N, 14.85.

2-(2,6-Dioxo(3-piperidyl))-4-{{[(ethylamino)thioxomethyl]amino}methyl}isindoline-1,3-dione I-114

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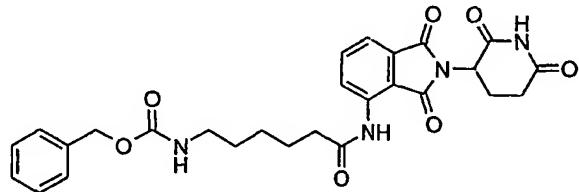


- 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29g, 1.90 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6g, 1.85 mmol) in CH₃CN (50 mL). After stirring for 20 min, ethyl

idothiocyanate (0.2g, 2.22 mmol) was added. The mixture was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (70 mL). The CH₂Cl₂ solution was washed with 2N HCl (30 mL), H₂O (30 mL), brine (30 mL) and dried (MgSO₄). The solvent was removed and the residue was purified by chromatography (SiO₂, CH₂Cl₂:EtOAc 6:4) to give 2-(2,6-dioxo(3-piperidyl))-4-({[(ethylamino)thioxomethyl]amino}methyl)isoindoline-1,3-dione (0.33g, 48%) as a white solid: mp 154-156°C; ¹H NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.86-7.66 (m, 5H), 5.19-5.09 (m, 3H), 3.38 (m, 2H), 2.98-2.83 (m, 1H), 2.64-2.50 (m, 2H), 2.08-2.04 (m, 1H), 1.09 (t, J=7.1 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.78, 169.85, 167.56, 167.02, 139.64, 134.53, 133.22, 131.54, 127.06, 121.76, 48.85, 42.74, 30.84, 22.80, 21.99, 14.32; Anal. Calcd. For C₁₇H₁₈N₄O₄S: C, 54.53; H, 4.85; N, 14.96; S, 8.56. Found: C, 54.89; H, 4.82; N, 14.72; S, 8.51.

{5-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylcarbamoyl]-pentyly-carbamic acid benzyl ester I-117}

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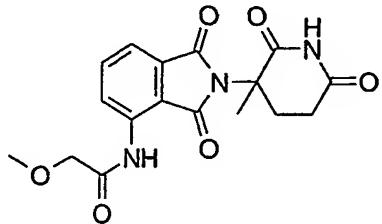


A solution of 6-benzyloxycarbonylamino-hexanoic acid(2.65 g, 10mmol) in thionyl chloride (15 ml) was heated to reflux 1h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated *in vacuo* to give (5-chlorocarbonyl-pentyl)-carbamic acid benzyl ester as tan oil. The oil was used without further purification. (5-Chlorocarbonyl-pentyl)-carbamic acid benzyl ester was dissolved in THF (50 ml). To this solution was added 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (1.37 g, 5 mmol). The resulting suspension was to reflux for 4 hours. The solvent was evaporated *in vacuo* and the resulting solid was partially purified by flash chromatography (60/40 ethyl acetate/hexane) to give a light yellow solid. The solid was recrystallized from minimal ethyl acetate to give 1.24 g (48%) of product as an off-white solid: mp 122-125 °C; ¹H NMR (DMSO-d₆) 11.18 (s, 1H), 9.70 (s, 1H), 8.49 (d, J=8.4 Hz, 1H), 7.83 (t, J=7.7 Hz, 1H), 7.61 (d, J=7.2 Hz, 1H), 7.34-7.24 (m, 6H), 5.16 (dd, J=5.1 and 12.6 Hz, 1H), 5.00 (s, 2H), 3.02-2.84 (m, 3H), 2.65-2.43 (m, 4H), 2.12-2.05 (m, 1H), 1.65-1.15 (m, 6H); ¹³C NMR (DMSO-d₆) 172.75, 171.95, 169.77, 167.72, 166.67, 156.08, 137.29, 136.57, 136.09, 131.43,

128.32, 127.70, 126.21, 118.25, 116.90, 65.08, 48.92, 36.47, 30.94, 30.67, 29.14, 25.77, 24.47, 21.99; Anal. Calcd. For C₂₇H₂₈N₄O₇: C, 62.30; H, 5.42; N, 10.76. Found: C, 62.40; H, 5.31; N, 10.48.

5 2-Methoxy-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide I-118

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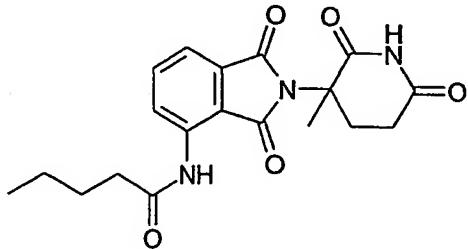
To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added methoxyacetyl chloride (0.08 g, 0.70 mmol).

- 15 The mixture was heated to reflux for 6 hours. The reaction mixture was allowed to cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.11 g (87 %) of product as an off-white solid: mp 244-246°C; ¹H NMR (DMSO-*d*₆) 11.07 (s, 1H), 10.26 (s, 1H), 8.68 (d, J=8.3 Hz, 1H), 7.82 (t, J=7.7 Hz, 1H), 7.55 (d, J=7.2 Hz, 1H), 4.10 (s, 2H), 3.47 (s, 3H), 2.77-2.51 (m, 3H), 2.09-2.04 (m, 1H), 1.90 (s, 3H); ¹³C NMR (DMSO-*d*₆) 172.12, 171.99, 169.15, 168.99, 167.38, 136.22, 135.68, 131.06, 124.25, 117.90, 115.91, 71.43, 59.06, 58.88, 29.01, 28.53, 20.92; Anal. Calcd. For C₂₁H₂₁N₃O₆: C, 56.48; H, 4.81; N, 11.62. Found: C, 56.10; H, 4.55; N, 11.39 + 0.12 H₂O.
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Pentanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide I-119

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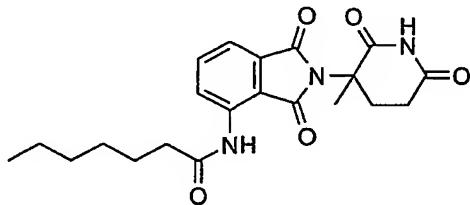


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To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added valeryl chloride (0.08 g, 0.70 mmol). The mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.11 g (81 %) of product as an off-white solid: mp 190-192 °C; ¹H NMR (DMSO-*d*₆) 11.04 (s, 1H), 9.65 (s, 1H), 8.50 (d, J=8.4 Hz, 1H), 7.79 (t, J=7.8 Hz, 1H), 7.52 (d, J=7.2 Hz, 1H), 2.74-2.44 (m, 5H), 2.10-2.03 (m, 1H), 1.90 (s, 3H), 1.66-1.54 (m, 2H), 1.42-1.27 (m, 2H), 0.91 (t, J=7.3 Hz, 3H); ¹³C NMR (DMSO-*d*₆) 172.13, 172.03, 168.75, 167.36, 136.42, 135.91, 131.20, 125.68, 117.71, 116.29, 58.81, 36.25, 29.07, 28.54, 26.83, 21.65, 20.98, 13.64; Anal. Calcd. For C₁₉H₂₁N₃O₅: C, 61.39; H, 5.70; N, 11.30. Found: C, 61.03; H, 5.51; N, 11.13 + 0.02 H₂O.

Heptanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide I-120

20

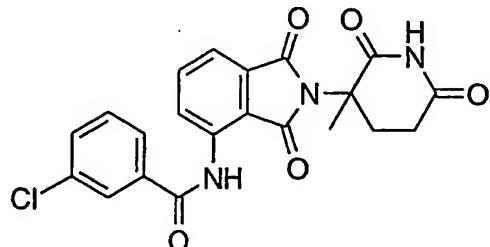


30

To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added heptanoyl chloride (0.10 g, 0.70 mmol). The mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.10 g (74 %) of product as an off-white solid: mp 172-174 °C; ¹H NMR (DMSO-*d*₆) 11.05 (s, 1H), 9.65 (s, 1H), 8.50 (d, J=8.3 Hz, 1H), 7.79 (t, J=7.6 Hz, 1H), 7.52 (d, J=7.2 Hz, 1H), 2.77-2.43 (m, 5H), 2.08-2.03 (m, 1H), 1.90 (s, 3H), 1.61 (t, J=6.4 Hz, 2H), 1.29 (bs, 6H), 0.87 (t, J=6.3 Hz, 3H); ¹³C NMR (DMSO-*d*₆) 172.12, 172.02, 168.74, 167.36, 136.41, 135.90, 131.20, 125.70, 117.71, 116.31, 58.81, 36.51, 30.93, 29.07, 28.54, 28.12, 24.69, 21.94, 20.98, 13.86; Anal. Calcd. For C₂₁H₂₅N₃O₅: C, 62.83; H, 6.33; N, 10.47. Found: C, 62.45; H, 6.18; N, 10.24 + 0.50 H₂O.

3-Chloro-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide I-121

5

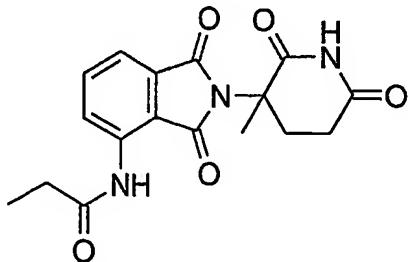


10

To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added 3-chlorobenzoyl chloride (0.12 g, 0.70 mmol). The mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.11 g (73 %) of product as an off-white solid: mp 283-285°C; ¹H NMR (DMSO-*d*₆) 11.06 (s, 1H), 10.43 (s, 1H), 8.48 (d, J=8.3 Hz, 1H), 7.98-7.61 (m, 6H), 2.80-2.51 (m, 3H), 2.11-2.01(m, 1H), 1.92 (s, 3H), 1.61 (t, J=6.4 Hz, 2H), 1.29 (bs, 6H), 0.87 (t, J=6.3 Hz, 3H); ¹³C NMR (DMSO-*d*₆) 171.72, 171.64, 168.53, 167.11, 163.55, 135.81, 135.75, 135.35, 133.59, 132.07, 131.03, 130.73, 127.03, 126.37, 125.58, 118.43, 118.06, 58.80, 28.90, 28.37, 20.84; Anal. Calcd. For C₂₁H₁₆ClN₃O₅: C, 59.23; H, 3.79; N, 9.87 Found: C, 59.00; H, 3.80; N, 9.70.

N-[2-(3-Methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-propionamide I-122

30



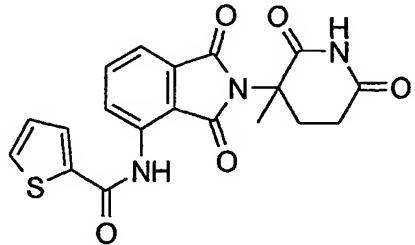
To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added propionyl chloride (0.07 g, 0.70 mmol).

The mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in diethyl ether (20 ml) and filtered to give 0.07 g (63 %) of product as an off-white solid: mp
 5 222-224 °C; ¹H NMR (DMSO-*d*₆) 11.03 (s, 1H), 9.63 (s, 1H), 8.51 (d, J=8.3 Hz, 1H), 7.79 (t, J=7.6 Hz, 1H), 7.51 (d, J=7.3 Hz, 1H), 2.76-2.45 (m, 5H), 2.10-2.03 (m, 1H), 1.90 (s, 3H), 1.12 (t, J=7.5 Hz, 3H); ¹³C NMR (DMSO-*d*₆) 172.70, 172.14, 172.03, 168.80, 167.37, 136.48, 135.94, 131.20, 125.59, 117.67, 116.21, 58.81, 29.71, 29.07, 28.53, 20.97, 14.74, 9.18; Anal. Calcd. For C₁₇H₁₇N₃O₅: C, 59.47; H, 4.99; N, 12.24 Found: C, 59.24; H, 5.06;
 10 N, 11.97.

Thiophene-2-carboxylic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide I-123

15

20

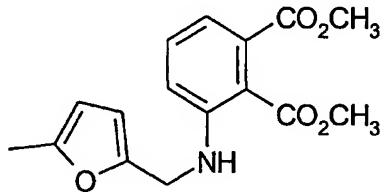


To a suspension of 4-amino-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione (0.10 g, 0.35 mmol) in THF (15 ml) was added 2-thiophenecarbonyl chloride (0.10 g, 0.70 mmol). The mixture was heated to reflux for 18 h. The reaction mixture was allowed to
 25 cool and to the solution was added methanol (2 ml). The reaction mixture was stirred for an additional 15 minutes followed by solvent evaporation *in vacuo*. The resulting solid was slurried in ethyl acetate (10 ml) and filtered to give 0.13 g of light yellow solid. The solid was recrystallized from acetonitrile to give 0.10 g of product (72%) as a off-white solid: mp 288-290 °C; ¹H NMR (DMSO-*d*₆) 11.07 (s, 1H), 10.32 (s, 1H), 8.49 (d, J=8.4 Hz, 1H), 7.98 (d, J=4.8 Hz, 1H), 7.89-7.83 (m, 2H), 7.59 (d, J=7.0 Hz, 1H), 7.31 (t, J=4.1 Hz, 1H), 2.80-2.51 (m, 3H), 2.12-2.01 (m, 1H), 1.92 (s, 3H); ¹³C NMR (DMSO-*d*₆) 172.10, 171.99, 169.00, 167.33, 159.60, 137.99, 136.05, 136.03, 133.26, 131.13, 129.82, 128.60, 125.91, 118.29, 117.43, 58.93, 29.04, 28.55, 20.96; Anal. Calcd. For C₁₉H₁₅N₃O₅S: C, 57.17; H, 3.84; N, 10.53 Found: C, 56.91; H, 3.48; N, 10.55 + 0.1 H₂O.

35

3-[(5-Methyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester

5

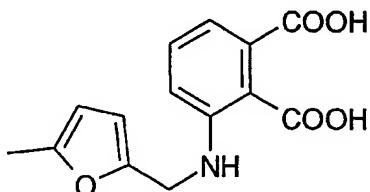


3-Amino-phthalic acid dimethyl ester (1.05 g, 5 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The

10 product of the reaction was used without further purification.

3-[(5-Methyl-furan-2-ylmethyl)-amino]-phthalic acid

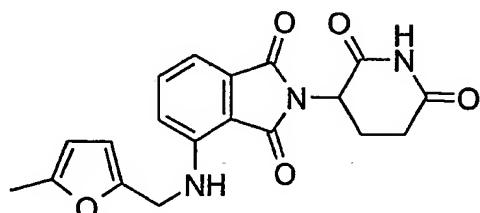
15



3-[(5-Methyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester (5 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

25 I-124
2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-methyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione

30



3-[(5-Methyl-furan-2-ylmethyl)-amino]-phthalic acid (5 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione. The residue was purified by preparative HPLC

(Symmetry C₁₈, isocratic, 35/65 acetonitrile/water) to give 0.31 g (20%) of product as a yellow solid: mp 305-307°C; ¹H NMR (DMSO-*d*₆) δ 11.10 (s, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.18 (d, J=8.6 Hz, 1H), 7.06 (d, J=7.1 Hz, 1H), 6.93 (t, J=6.0 Hz, 1H), 6.22 (d, J=2.9 Hz, 1H), 5.98 (d, J=1.9 Hz, 1H), 5.07 (dd, J= 5.3 and 12.5 Hz, 1H), 4.49 (d, J=6.0 Hz, 2H), 5 2.97-2.82 (m, 1 H), 2.62-2.44 (m, 2H), 2.22 (s, 3H), 2.06-1.99 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.77, 170.02, 168.77, 167.21, 151.04, 150.02, 145.80, 136.04, 132.08, 117.57, 110.96, 109.63, 108.27, 106.34, 48.55, 38.94, 30.95, 22.10, 13.24; Anal. Calcd. For C₁₉H₁₇N₃O₅: C, 62.12; H, 4.66; N, 11.44. Found: C, 61.75; H, 4.71; N, 11.15.

10 3-[(5-Hydroxymethyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester

15



5-Hydroxymethyl-furan-2-carbaldehyde (0.95 ml, 7.5 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester.

20 The residue (oil) was purified by chromatography (SiO₂, 40/60 ethyl acetate/hexanes) to give 0.97 g (76%) of yellow oil: ¹H NMR (CDCl₃) δ 7.35-7.27 (m, 1H), 7.05 (bs, 1H), 6.87-6.83 (m, 2H), 6.21 (d, J=3.1 Hz, 1H), 6.17 (d, J=3.2 Hz, 1H), 4.57 (s, 2H), 4.38 (bs, 2H) 3.86 (s, 3H), 3.83 (s, 3H), 1.98 (bs, 1H).

25 3-[(5-Hydroxymethyl-furan-2-ylmethyl)-amino]-phthalic acid

30

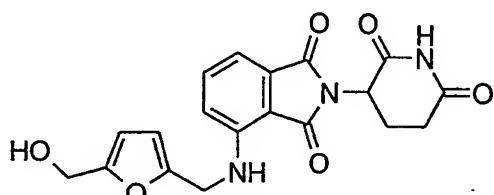


35 3-[(5-Hydroxymethyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester (0.97 g, 3.04 mmol) was treated in the same manner as described above for the synthesis of 3-(2-

methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-hydroxymethyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione I-125

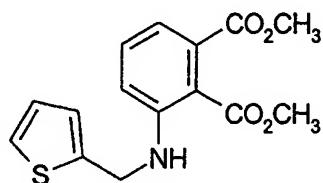
10



3-[(5-Hydroxymethyl-furan-2-ylmethyl)-amino]-phthalic acid (3.04 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-Dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione. The solid yellow residue was purified by chromatography (SiO_2 , 60% ethyl acetate/hexanes) to give 0.40 g of solid which was dissolved in methylene chloride (70 ml) and washed with saturated NaHCO_3 (2 x 100 ml), brine (1 x 100 ml), dried (magnesium sulfate), and filtered. The solvent was evaporated leaving 0.32 g (27%) of product as a yellow solid: mp 172-174°C; ^1H NMR ($\text{DMSO}-d_6$) δ 11.11 (s, 1H), 7.58 (t, $J=7.9$ Hz, 1H), 7.18 (d, $J=8.6$ Hz, 1H), 7.06 (d, $J=7.0$ Hz, 1H), 6.99 (t, $J=6.0$ Hz, 1H), 6.27 (d, $J=2.9$ Hz, 1H), 6.20 (d, $J=2.9$ Hz, 1H), 5.18 (t, $J=5.7$ Hz, 1H), 5.07 (dd, $J=5.2$ and 12.5 Hz, 1H), 4.54 (d, $J=5.9$ Hz, 2H), 4.33 (d, $J=5.7$ Hz, 2H), 2.96-2.82 (m, 1H), 2.63-2.46 (m, 2H), 2.06-1.99 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 172.80, 170.07, 168.80, 167.24, 155.00, 151.10, 145.79, 136.08, 132.12, 117.57, 111.04, 109.71, 108.06, 107.60, 55.63, 48.60, 39.05, 30.98, 22.13; Anal. Calcd. For $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.30; H, 4.54; N, 10.70.

3-[(Thiophen-2-ylmethyl)-amino]-phthalic acid dimethyl ester

30

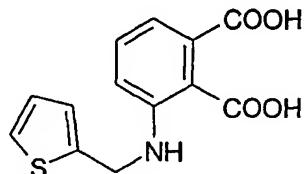


35

2-Thiophenecarboxaldehyde (1.12 g, 10 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The residue (oil) was purified by preparative HPLC (Symmetry C₁₈, isocratic, 45% acetonitrile/water) to give 0.88 g (58%) of yellow oil: ¹H NMR (CDCl₃) δ 7.38-7.15 (m, 3H), 7.00-6.93 (m, 2H), 6.87-6.82 (m, 2H), 4.58 (d, J=5.3 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H).

3-[(Thiophen-2-ylmethyl)-amino]-phthalic acid

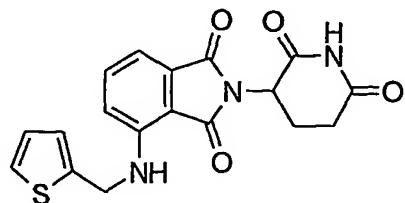
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15 3-[(Thiophen-2-ylmethyl)-amino]-phthalic acid dimethyl ester (0.88 g, 2.88 mmol) was treated in the same manner as described above for the synthesis 3-(2-methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

20 2-(2,6-Dioxo-piperidin-3-yl)-4-[(thiophen-2-ylmethyl)-amino]-isoindole-1,3-dione I-126

25

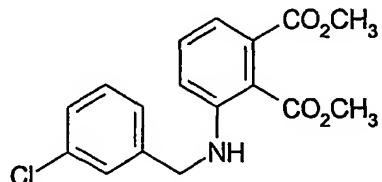


30 3-[(Thiophen-2-ylmethyl)-amino]-phthalic acid (2.88 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione. The solid yellow residue was purified by preparative HPLC (Symmetry C₁₈, isocratic, 35% acetonitrile/water) to give 0.31 g (29%) of product as a yellow solid: mp 223-225°C; ¹H NMR (DMSO-d₆) δ 11.12 (s, 1H), 7.56 (t, J=7.8 Hz, 1H), 7.39 (d, J=4.8 Hz, 1H), 7.23-6.96 (m, 5H), 5.07 (dd, J= 5.3 and 12.4 Hz, 1H), 4.75 (d, J=6.0 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.46 (m, 2H), 2.09-1.99 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.77, 170.03, 168.67, 167.20, 145.60, 142.51, 136.04, 132.15, 126.88,

125.40, 125.00, 117.67, 111.05, 109.80, 48.56, 40.88, 30.96, 22.10; Anal. Calcd. For C₁₈H₁₅N₃O₄S: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.20; H, 3.96; N, 10.99.

3-(3-Chloro-benzylamino)-phthalic acid dimethyl ester

5



10 3-Chlorobenzacetaldehyde (1.14 ml, 10 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The residue (oil) was purified by chromatography (SiO₂, 15% ethyl acetate/hexanes) to give 1.61 g (96%) of yellow oil: ¹H NMR (CDCl₃) δ 7.35-7.18 (m, 6), 6.83 (d, J=7.4 Hz, 1H), 6.65 (d, J=8.5 Hz, 1H), 4.39 (d, J=5.8 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H).

15

3-(3-Chloro-benzylamino)-phthalic acid

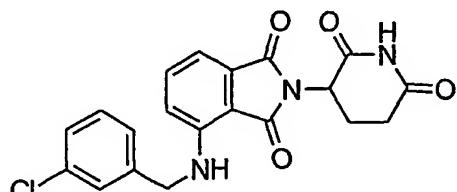
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3-(3-Chloro-benzylamino)-phthalic acid dimethyl ester (1.61 g, 4.8 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

4-(3-Chloro-benzylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione I-127

30

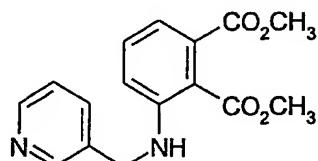


35

- 3-(3-Chloro-benzylamino)-phthalic acid (4.8 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione. The solid yellow residue was slurried in diethyl ether (30 ml) for 18 h and filtered to give 1.42 g (89 %) of product as a yellow solid: mp 207-209°C;
- 5 ¹H NMR (DMSO-*d*₆) δ 11.11 (s, 1H), 7.55-7.28 (m, 6H), 7.03 (d, J=7.0 Hz, 1H), 6.95 (d, J=8.6 Hz, 1H), 5.08 (dd, J= 5.4 and 12.4 Hz, 1H), 4.58 (d, J=6.3 Hz, 2H), 2.98-2.83 (m, 1 H), 2.64-2.46 (m, 2H), 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.56, 169.84, 168.59, 167.11, 145.76, 141.68, 136.01, 133.10, 132.16, 130.25, 126.83, 126.68, 125.48, 117.40, 110.81, 109.74, 48.54, 41.54, 44.80, 30.87, 22.05; Anal. Calcd. For C₂₀H₁₆ClN₃O₄: C, 60.38; H, 4.05; N, 10.56. Found: C, 60.22; H, 4.05; N, 10.38.
- 10

3-[(Pyridin-3-ylmethyl)-amino]-phthalic acid dimethyl ester

15



- 20 3-Pyridinecarboxaldehyde (0.94 ml, 10 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. After removal of pyridine the residue was dissolved in methylene chloride (100 ml) and washed with water (2 x 100 ml), saturated NaHCO₃ (2 x 100ml), brine (1 x 100 ml), dried (magnesium sulfate), and filtered. The solvent was evaporated *in vacuo* to give an oil. The oil was dissolved in
- 25 diethyl ether (100 ml) and extracted with 0.1 N HCl (2 x 100 ml). The combined aqueous HCl extracts were washed with diethyl ether (2 x 100 ml) and the pH adjusted to 10 by dropwise addition of saturated Na₂CO₃. The product was extracted with diethyl ether (3 x 100 ml). The combined ether extracts were washed with brine (1 x 100 ml), dried (magnesium sulfate), and filtered. The solvent was evaporated *in vacuo* to give 0.91 g (61
- 30 %) of product as a light yellow oil which was used without further purification: ¹H NMR (CDCl₃) δ 8.61 (d, J=2.0 Hz, 1H), 8.53 (dd, J=1.1 Hz and 4.8 Hz, 1H), 7.65 (d, J=7.9 Hz, 1H), 7.31-7.21 (m, 3H), 6.85 (d, J=7.3 Hz, 1H), 6.69 (d, J=8.5 Hz, 1H), 4.45 (d, J=5.7 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H).

35

3-[(Pyridin-3-ylmethyl)-amino]-phthalic acid

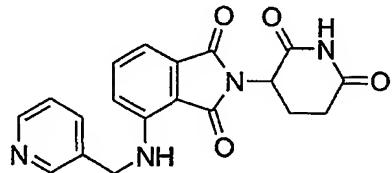
5



3-[(Pyridin-3-ylmethyl)-amino]-phthalic acid dimethyl ester (0.91 g, 3.03 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-ethylamino)-
10 phthalic acid except the pH of crude reaction mixture was adjusted to 2-3 by dropwise addition of concentrated HCl. The solvent was then evaporated *in vacuo* leaving a dry salt mixture that was used without further purification.

15 2-(2,6-Dioxo-piperidin-3-yl)-4-[(pyridin-3-ylmethyl)-amino]-isoindole-1,3-dione I-128

20

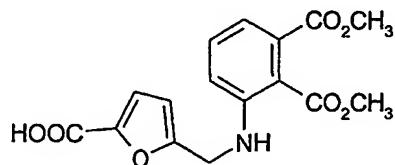


3-[(Pyridin-3-ylmethyl)-amino]-phthalic acid (3.03 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxy-
25 ethylamino)-isoindole-1,3-dione. The solid yellow residue was slurried in 50% methanol/ethyl acetate (20 ml) for 18 h to give 0.50 g (46%) of product as a yellow solid: mp 231-233 °C; ¹H NMR (DMSO-*d*₆) δ 11.14 (s, 1H), 8.63 (s, 1H), 8.47 (s, 1H), 7.78 (d, J=7.7 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.39-7.30 (m, 2H), 7.03 (t, J=6.6 Hz, 2H), 5.09 (dd, J= 5.2 and 12.4 Hz, 1H), 4.61 (d, J=6.0 Hz, 2H), 2.97-2.84 (m, 1 H), 2.64-2.48 (m, 2H),
30 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.78, 170.05, 168.65, 167.22, 148.66, 148.27, 145.75, 136.14, 134.79, 134.54, 132.25, 123.58, 117.50, 110.92, 109.82, 48.57, 42.99, 30.96, 22.12; Anal. Calcd. For C₁₉H₁₆N₄O₄: C, 62.63; H, 4.43; N, 15.38. Found: C, 62.30; H, 4.27; N, 15.30.

35

3-[(5-Carboxy-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester

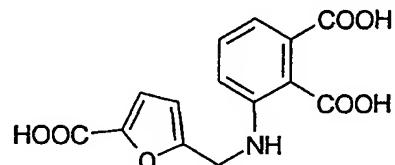
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5-Formyl-furan-2-carboxylic acid (1 g, 7.14 mmol) was treated in the same manner as
 10 described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester except the combined aqueous NaHCO₃ extracts were washed with methylene chloride (1 x 70 ml) and the pH adjusted to 2-3 by dropwise addition of concentrated HCl. The mixture was then extracted with ethyl acetate (3 x 75 ml). The combined ethyl acetate extracts were washed with brine (1 x 100 ml), dried (magnesium sulfate), and filtered. The solvent was
 15 evaporated *in vacuo* to give 0.90 g product as an off-white solid: ¹H NMR (CDCl₃) δ 7.42-7.36 (m, 1H), 7.16 (d, J=3.5 Hz, 1H), 7.03-6.97 (m, 2H), 6.90 (dd, J=1.0 Hz and 7.3 Hz, 1H), 6.48 (d, J=3.5 Hz, 1H), 4.60 (d, J=5.2 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H).

3-[(5-Carboxy-furan-2-ylmethyl)-amino]-phthalic acid

20



25 3-[(5-Carboxy-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester (0.90 g, 2.70 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxyethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

30

35

5-{[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylamino]-methyl}-furan-2-carboxylic acid I-129

5

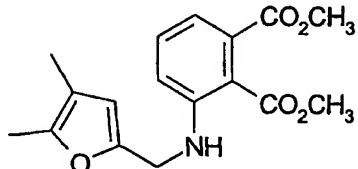


3-[(5-Carboxy-furan-2-ylmethyl)-amino]-phthalic acid (1.78 g, 5.65 mmol) was treated in
 10 the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione. The solid yellow residue was purified by preparative HPLC (Symmetry, C₁₈, isocratic, 30% acetonitrile/water) to give 0.39 g (36%) of product as a yellow solid: mp 202-204°C; ¹H NMR (DMSO-*d*₆) δ 13.01 (bs, 1H), 11.11 (s, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.17-7.07 (m, 4H), 6.51 (d, J=3.2 Hz, 1H), 5.08 (dd, J=5.2 Hz and 12.4 Hz, 1H), 4.65 (d, J=5.9 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.47 (m, 2H), 2.07-2.03 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.78, 170.02, 168.65, 167.20, 159.13, 156.61, 145.58, 144.19, 136.13, 132.17, 118.59, 117.52, 111.24, 109.97, 109.55, 48.59, 30.96, 22.11; Anal. Calcd. For C₁₉H₁₅N₃O₇: C, 56.76; H, 3.89; N, 10.45. Found: C, 56.53; H, 4.16; N, 10.24 + 1.18% H₂O.

20

3-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester

25



4,5-Dimethyl-furan-2-carbaldehyde (0.98 ml, 8 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The residue (oil) was purified by chromatography (SiO₂, 10% ethyl acetate/hexanes) to give 0.95
 30 g (75%) of product as a yellow oil: ¹H NMR (CDCl₃) δ 7.32 (t, J=8.2 Hz, 1H), 6.97 (bs, 1H), 6.88-6.83 (m, 2H), 5.99 (s, 1H), 4.28 (d, J=5.5 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.17 (s, 3H), 1.87 (s, 3H).

35

3-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-phthalic acid

5



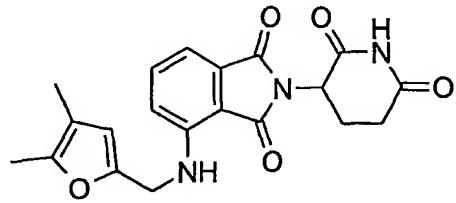
3-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-phthalic acid dimethyl ester (0.95 g, 3 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxy-

10 ethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

4-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione I-130

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20



3-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-phthalic acid (3 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione. The solid yellow residue was purified by preparative

25 HPLC (Symmetry C₁₈, isocratic, 40% acetonitrile/water) to give 0.25 g (22%) of product as a yellow solid: mp 127-129°C; ¹H NMR (DMSO-*d*₆) δ 11.10 (s, 1H), 7.58 (dd, J=7.4 Hz and 8.4 Hz, 1H), 7.17 (d, J=8.6 Hz, 1H), 7.06 (d, J=7.1 Hz, 1H), 6.91 (t, J=6.1 Hz, 1H), 5.11 (s, 1H), 5.06 (dd, J= 5.4 and 12.5 Hz, 1H), 4.45 (d, J=6.0 Hz, 2H), 2.97-2.82 (m, 1 H), 2.63-2.44 (m, 2H), 2.13 (s, 3H), 2.08-1.99 (m, 1H), 1.85 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 172.75, 170.02, 168.77, 167.21, 148.75, 146.18, 145.82, 136.05, 132.07, 117.57, 114.16,

30 110.94, 110.55, 109.61, 48.56, 38.94, 30.95, 22.10, 11.08, 9.50; Anal. Calcd. For C₂₀H₁₉N₃O₅: C, 62.99; H, 5.02; N, 11.02. Found: C, 62.75; H, 4.97; N, 10.72.

35

3-[(Benzofuran-2-ylmethyl)-amino]-phthalic acid dimethyl ester

5



Benzofuran-2-carbaldehyde (1.17 ml, 8 mmol) was treated in the same manner as described above for the synthesis of 3-pentylamino-phthalic acid dimethyl ester. The residue (oil) was purified by chromatography (SiO₂, 50% methylene chloride/hexane) to give 1.12 g (83%) of product as a yellow oil: ¹H NMR (CDCl₃) δ 7.50-7.43 (m, 2H), 7.33-7.16 (m, 3H), 6.88-6.84 (m, 2H), 6.58 (s, 1H), 4.54 (d, J=6.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H).

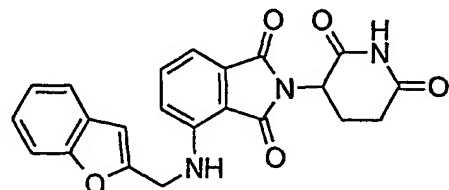
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3-[(Benzofuran-2-ylmethyl)-amino]-phthalic acid

20 3-[(Benzofuran-2-ylmethyl)-amino]-phthalic acid dimethyl ester (1.12 g, 3.3 mmol) was treated in the same manner as described above for the synthesis of 3-(2-methoxyethylamino)-phthalic acid. The product of the reaction, which contained a mixture of diacid and monomethyl esters, was used without further purification.

25 4-[(Benzofuran-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione I-131

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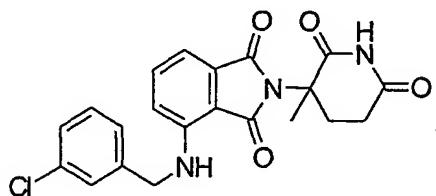


3-[(Benzofuran-2-ylmethyl)-amino]-phthalic acid (3.3 mmol) was treated in the same manner as described above for the synthesis of 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxyethylamino)-isoindole-1,3-dione. The solid yellow residue was slurried in methylene chloride (20 ml) for 18 h and filtered to give 0.59 g (37%) of product as a yellow solid: mp

199-201 °C; ^1H NMR (DMSO- d_6) δ 11.14 (s, 1H), 7.61-7.52 (m, 3H), 7.29-7.18 (m, 4H), 7.08 (d, J=7.0 Hz, 1H), 6.80 (s, 1H), 5.10 (dd, J= 5.4 and 12.5 Hz, 1H), 4.77 (d, J=6.1 Hz, 2H), 2.98-2.83 (m, 1 H), 2.64-2.46 (m, 2H), 2.07-2.03 (m, 1H); ^{13}C NMR (DMSO- d_6) δ 172.76, 170.02, 168.71, 167.20, 155.33, 154.33, 154.22, 145.71, 136.09, 132.15, 127.93, 5 123.96, 122.81, 120.88, 117.64, 111.19, 110.93, 109.96, 103.85, 48.59, 30.96, 22.12; Anal. Calcd. For $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_5$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.35; H, 4.12; N, 10.34.

4-(3-Chloro-benzylamino)-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione I-132

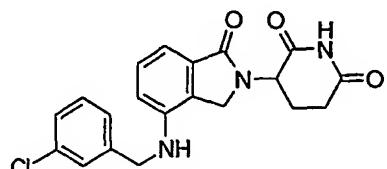
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15 To a stirred solution of 3-(3-Chloro-benzylamino)-phthalic acid (4 mmol) in pyridine (50 ml) was added 3-amino-3-methyl-piperidine-2,6-dione hydrochloride (0.71 g, 4 mmol). The reaction mixture was heated to reflux for 18 h. The solvent was evaporated *in vacuo* and the residue dissolved in methylene chloride (150 ml). The methylene chloride mixture was washed with water (2 x 100 ml), 0.1N HCl (2 x 100 ml), brine (1 x 100 ml), dried 20 (magnesium sulfate), and filtered. The solvent was evaporated *in vacuo* to give a yellow semi-solid. The residue was purified by preparative HPLC (Symmetry C₁₈, isocratic, 50% acetonitrile/water) to give 0.67 g (41%) of product as a yellow solid: mp 199-201 °C; ^1H NMR (DMSO- d_6) δ 10.99 (s, 1H), 7.52-7.28 (m, 6H), 6.97-6.89 (m, 2H), 4.54 (d, J=6.1 Hz, 1H), 2.78-2.50 (m, 3H), 2.08-1.98 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 172.42, 25 172.19, 169.62, 167.92, 145.59, 141.82, 136.02, 133.14, 132.06, 130.35, 126.91, 126.78, 125.60, 117.23, 110.42, 109.49, 58.37, 44.74, 29.27, 28.62, 21.02; Anal. Calcd. For $\text{C}_{21}\text{H}_{18}\text{ClN}_3\text{O}_4$: C, 61.24; H, 4.41; N, 10.20. Found: C, 61.30; H, 4.28; N, 9.97.

3-[4-(3-Chloro-benzylamino)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione I-133

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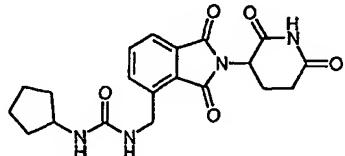
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3-(4-Amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (1.04 g, 4 mmol) was dissolved in acetic acid (7 ml) with heat. The mixture was cooled slightly and methylene chloride (50 ml) was added slowly followed by 3-chlorobenzaldehyde (0.91 ml, 8 mmol) and sodium triacetoxyborohydride (2.54 g, 12 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 2 h, diluted with methylene chloride (100 ml), washed with water (2 x 100 ml), saturated aqueous sodium bicarbonate (2 x 100 ml), brine (100 ml), dried (magnesium sulfate), and filtered. The solvent was evaporated *in vacuo* to give a white solid. The solid was recrystallized from methylene chloride/methanol to give 0.48 g (31%) of product as a white solid: mp 253-255 °C; ¹H NMR (DMSO-*d*₆) δ 11.05 (s, 1H), 7.45 (s, 1H), 7.37-7.19 (m, 4H), 6.95 (d, J=7.4 Hz, 1H), 6.63 (d, J=8.0 Hz, 1H), 6.45 (t, J=5.9 Hz, 1H), 5.14 (dd, J= 5.1 and 13.1 Hz, 1H), 4.41 (d, J=5.8 Hz, 2H), 4.34 (d, J=17.3 Hz, 1H), 4.20 (d, J=17.2 Hz, 1H) 3.01-2.87 (m, 1H), 2.66-2.60 (m, 1H), 2.42-2.25 (m, 1 H), 2.08-2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 172.90, 171.24, 168.74, 143.03, 142.59, 133.08, 132.16, 130.19, 129.12, 126.80, 126.70, 125.73, 112.27, 110.55, 51.54, 45.73, 45.47, 31.25, 22.79; Anal. Calcd. For C₂₀H₁₈ClN₃O₃: C, 62.58, H, 4.73; N, 10.95. Found: C, 62.32; H, 4.61; N, 10.80.

N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclopentylamino)carboxamide I-134

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25



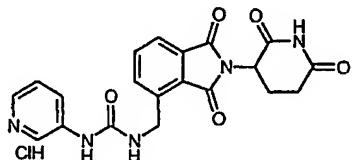
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29 g, 1.9 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in acetonitrile (50 mL). After stirring for 20 min, 4-nitrophenyl-N-30 cyclopentylcarbamate (0.44 g, 1.85 mmol) was added. The mixture was stirred at room temperature for 17 hours. The mixture was filtered to afford N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclopentylamino)carboxamide (0.2 g, 27%) as a white solid: mp 151-153 °C; ¹H NMR (DMSO-*d*₆) δ 11.13 (s, 1H), 7.86-7.68 (m, 3H), 6.31 (t, 1H), 6.17 (d, J=6.9 Hz, 1H), 5.18-5.11 (dd, J=4.6 and 12.3 Hz, 1H), 4.62 (d, J=5.4 Hz, 2H), 3.83 (q, J=6.4 Hz, 2H), 2.96-2.85 (m, 1H), 2.64-2.50 (m, 2H), 2.07-2.04 (m, 1H),

1.70-1.29 (m, 8H); ^{13}C NMR (DMSO-d₆) δ 172.77, 169.83, 167.59, 167.04, 157.63, 141.12, 134.64, 133.43, 131.52, 128.99, 121.64, 51.09, 48.83, 38.70, 32.91, 30.94, 23.16, 21.99; Anal. Calcd. For C₂₀H₂₂N₄O₅: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.09; H, 5.66; N, 14.15.

5

N-{{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(3-pyridylamino)carboxamide Hydrochloride I-135

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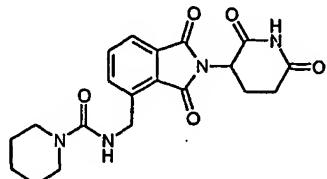
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.29 g, 1.9 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.85 mmol) in acetonitrile (50 mL). After stirring for 20 min, (2,5-dioxopyrrolidinyloxy)-N-(3-pyridyl)carboxamide (0.44 g, 1.85 mmol) was added. The mixture was stirred at room temperature for 17 hours. The mixture was filtered and the solid was recrystallized from methanol (25 mL) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(3-pyridylamino)carboxamide (0.23 g, 30%). 2N HCl/ether was added to a stirred solution of N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(3-pyridylamino)carboxamide (0.23 g) in methanol (5 mL) and ethyl acetate (10 mL). The mixture was stirred for 2 hours and filtered to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(3-pyridylamino)carboxamide hydrochloride (0.2 g) as a white solid: mp 263-265 °C; ^1H NMR (DMSO-d₆) δ 11.17 (s, 1H), 10.43 (s, 1H), 9.08 (d, J=1.7 Hz, 1H), 8.44 (d, J=5.4 Hz, 1H), 8.33-8.29 (dd, J=1.2 and 8.5 Hz, 1H), 7.93-7.78 (m, 4H), 7.55 (t, J=6.0 Hz, 1H), 5.21-5.14 (dd, J=5.0 and 12.5 Hz, 1H), 4.80 (d, J=5.9 Hz, 2H), 2.97-2.84 (m, 1H), 2.65-2.50 (m, 2H), 2.10-2.06 (m, 1H); ^{13}C NMR (DMSO-d₆) δ 172.78, 169.83, 167.54, 166.96, 154.78, 139.97, 139.51, 134.80, 134.37, 133.35, 132.34, 131.60, 130.43, 127.17, 127.10, 121.99, 48.88, 38.68, 30.94, 21.99; Anal. Calcd. For C₂₀H₁₈N₅O₅Cl: C, 54.12; H, 4.09; N, 15.78; Cl, 7.99. Found: C, 54.11; H, 4.10; N, 15.44; Cl, 7.81.

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N-{{[2,(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}piperidylcarboxamide I-136}

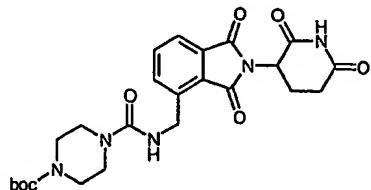
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Diisopropylethylamine (0.88 g, 6.79 mmol) was added to a stirred suspension of 4-
 10 (aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (1.0 g, 3.09
 mmol) in acetonitrile (50 mL). After stirring for 20 min, the mixture was slowly added to a
 stirred solution of triphosgene (0.34 g, 1.14 mmol) in acetonitrile (15 mL) over 30 min.
 After a further 10 min of stirring, a solution of piperidine (0.26 g, 3.09 mmol) and
 diisopropylethylamine (0.48 g, 3.71 mmol) in acetonitrile (10 mL) was added in one
 15 portion. The mixture was stirred at room temperature for 17 hours. The mixture was
 concentrated and the residue was dissolved in methylene chloride (80 mL). The methylene
 chloride solution was washed with 10% KHSO₄ (30 mL), H₂O (2x30 mL), brine (30 mL)
 and dried (MgSO₄). Solvent was removed and the residue was purified by chromatography
 (CH₂Cl₂: CH₃OH 97.5:2.5) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-
 20 yl]methyl}piperidylcarboxamide (0.66 g, 53%) as a white solid: mp 156-158°C; ¹H NMR
 (DMSO-d₆) δ 11.14 (s, 1H), 7.86-7.75 (m, 2H), 7.69 (d, J=7.4 Hz, 1H), 7.12 (t, J=5.6 Hz,
 1H), 5.18-5.11 (dd, J=5.3 and 12.5 Hz, 1H), 4.69 (d, J=5.5 Hz, 2H), 3.42-3.32 (m, 4H),
 2.96-2.83 (m, 1H), 2.63-2.50 (m, 2H), 2.08-2.03 (m, 1H), 1.54-1.44 (m, 6H); ¹³C NMR
 (DMSO-d₆) δ 172.74, 169.83, 167.60, 157.26, 141.46, 134.58, 132.82, 131.38, 126.74,
 25 121.43, 48.82, 44.37, 30.93, 25.37, 24.12, 21.98; Anal. Calcd. For C₂₀H₂₂N₄O₅+0.22 H₂O:
 C, 59.70; H, 5.62; N, 13.92. Found: C, 60.14; H, 5.59; N, 13.47.

Tert-Butyl 4-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-
 yl]methyl}(carbamoyl)piperazinecarboxylate I-137

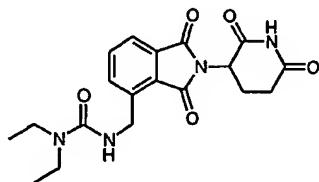
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- Diisopropylethylamine (1.05 g, 8.16 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (1.2 g, 3.71 mmol). After stirring for 20 min, the mixture was added slowly to a stirred solution of triphosgene (0.41 g, 1.37 mmol) in acetonitrile (20 mL) over 30 min. After a further 10 min
- 5 of stirring, a solution of t-BOC-1-piperazine carboxylate (0.69 g, 3.71 mmol) and diisopropylethylamine (0.58 g, 4.45 mmol) in acetonitrile (10 mL) was added in one portion. The mixture was stirred at room temperature for 17 hours. The mixture was concentrated and the residue was dissolved in methylene chloride (100 mL). The methylene chloride solution was washed with water (2x40 mL), brine (40 mL) and dried (MgSO_4).
- 10 Solvent was removed and the residue was purified by chromatography (CH_2Cl_2 : CH_3OH 97.5:2.5) to give tert-butyl 4-(N- $\{\text{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}\}$ (carbamoyl)piperazinecarboxylate (0.98 g, 52%) as a white solid: mp 158-160°C; ^1H NMR (DMSO-d_6) δ 11.14 (s, 1H), 7.86-7.69 (m, 3H), 7.27 (t, $J=5.5$ Hz, 1H), 5.18-5.11 (dd, $J=5.4$ and 12.5 Hz, 1H), 4.71 (d, $J=5.4$ Hz, 2H), 3.33 (s, 8H), 2.98-2.83 (m, 1H), 2.63-
- 15 2.49 (m, 2H), 2.08-2.04 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 172.74, 170.04, 169.83, 167.58, 167.03, 157.30, 153.86, 140.99, 136.52, 134.64, 132.94, 131.39, 126.80, 121.53, 111.33, 79.03, 74.43, 48.82, 43.22, 30.92, 28.03, 21.98; Anal. Calcd. For $\text{C}_{24}\text{H}_{29}\text{N}_5\text{O}_7+0.13\text{H}_2\text{O}$: C, 57.44; H, 5.88; N, 13.95. Found : C, 57.83; H, 6.09; N, 13.45.
- 20 N- $\{\text{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}\}$ (diethylamino)carboxamide I-138

25



- Diisopropylethylamine (0.88 g, 6.80 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (1.0 g, 3.09 mmol) in acetonitrile (50 mL). After stirring for 20 min, the mixture was slowly added to a stirred solution of triphosgene (0.34 g, 1.14 mmol) in acetonitrile (20 mL) over 20 min. After a further 10 min of stirring, a solution of diethylamine (0.23 g, 3.09 mmol) and diisopropylethylamine (0.48 g, 3.71 mmol) in acetonitrile (10 mL) was added in one portion. The mixture was stirred at room temperature for 17 hours. The mixture was
- 30 concentrated and the residue was dissolved in methylene chloride (80 mL). The methylene
- 35

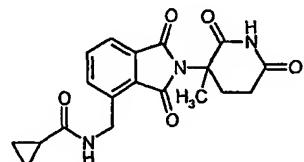
chloride solution was washed with 1N HCl (40 mL), H₂O (2x40 mL), brine (40 mL) and dried (MgSO₄). Solvent was removed and the residue was purified by chromatography (CH₂Cl₂: CH₃OH 97.5:2.5) to afford N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}(diethylamino)carboxamide (0.8 g, 67%) as a white solid: mp 142-144°C; ¹H

5 NMR (DMSO-d₆) δ 11.14 (s, 1H), 7.86-7.66 (m, 3H), 6.91 (t, J=5.7 Hz, 1H), 5.19-5.12 (dd, J=5.4 and 12.6 Hz, 1H), 4.70 (d, J=5.6 Hz, 2H), 3.26 (q, J=6.9 Hz, 4H), 2.98-2.83 (m, 1H), 2.64-2.49 (m, 2H), 2.08-2.04 (m, 1H), 1.06 (t, J=7.0 Hz, 6H); ¹³C NMR (DMSO-d₆) δ 172.73, 169.81, 167.63, 167.04, 156.74, 134.54, 132.80, 131.38, 126.72, 121.38, 48.82, 40.24, 30.92, 21.97, 13.90; Anal. Calcd. For C₁₉H₂₂N₄O₅: C, 59.06; H, 5.74; N, 14.50.

10 Found: C, 58.71; H, 5.76; N, 14.10.

Cyclopropyl-N-{{[2-(3-methyl-2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}carboxamide I-139}

15



1,8-Diazabicyclo[5.4.0]undec-7-ene (0.68 g, 4.44 mmol) was added to a stirred suspension
20 of 4-(aminomethyl)-2-(3-methyl-2,6-dioxo(3-piperidyl))isoindoline-1,3-dione hydrochloride (0.6 g, 1.78 mmol) in acetonitrile (50 mL). After stirring for 20 min, cyclopropanecarbonyl chloride (0.22 g, 2.14 mmol) was added. The mixture was stirred at room temperature for 17 hours. The mixture was filtered and the solid was washed with acetonitrile (10 mL) to give cyclopropyl-N-{{[2-(3-methyl-2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]methyl}carboxamide (0.49 g, 74%) as a white solid: mp 243-245°C; ¹H NMR (DMSO-d₆) δ 11.04 (s, 1H), 8.68 (t, J=5.8 Hz, 1H), 7.84-7.63 (m, 3H), 5.76 (s, 1H), 4.70 (d, J=5.8 Hz, 2H), 2.71-2.54 (m, 2H), 2.10-2.02 (m, 1H), 1.90 (s, 3H), 1.68-1.63 (, 1H), 0.71-0.68 (m, 4H); ¹³C NMR (DMSO-d₆) δ 173.07, 172.20, 172.15, 168.29, 167.68, 139.01, 134.61, 133.19, 131.40, 126.78, 121.50, 58.71, 54.88, 37.72, 29.09, 28.57, 21.00, 13.51, 6.42; Anal.
25 Calcd. For C₁₉H₁₉N₃O₅: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.53; H, 5.20; N, 11.39.

Methyl 3-bromo-2-methylbenzoate

A mixture of 3-bromo-2-methylbenzoic acid (16 g, 74.4 mmol), sodium bicarbonate (12.5 g, 148.8 mmol) and iodomethane (21.2 g, 148.8 mmol) in DMF (160 mL) was heated at 60°C
35 for 2 hours. The mixture was cooled to room temperature and poured into ice water (400

mL). The mixture was extracted with ethyl acetate (4x100 mL). The EtOAc solution was washed with water (3x100 mL), brine (100 mL) and dried (MgSO_4). Solvent was removed to give methyl 3-bromo-2-methylbenzoate (17.6 g, 100%) as an oil: $^1\text{H NMR}$ (CDCl_3) δ 7.70 (t, $J=7.6$ Hz, 2H), 7.08 (t, $J=7.9$ Hz, 1H), 3.90 (s, 3H), 2.67 (s, 3H).

5

Methyl 3-bromo-2-bromomethylbenzoate

A mixture of methyl 3-bromo-2-methylbenzoate (17.0 g, 74.22 mmol) and N-bromosuccinimide (15.85 g, 89.06 mmol) in acetonitrile (200 mL) was heated under gently refluxing for 17 hours while a 200W bulb situated 2 cm away was shining on the reaction 10 flask. The mixture was cooled to room temperature and solvent was removed. The residue was dissolved in ethyl acetate (200 mL) and washed with water (3x80 mL), brine (80 mL) and dried (MgSO_4). Solvent was removed to give methyl 3-bromo-2-bromomethylbenzoate (24.5 g, 97% by HPLC): $^1\text{H NMR}$ (CDCl_3) δ 7.90-7.86 (dd, $J=1.0$ and 7.9 Hz, 1H), 7.78-7.74 (dd, $J=1.2$ and 8.2 Hz, 1H), 7.22 (t, $J=7.9$ Hz, 1H), 5.12 (s, 2H), 3.95 (s, 3H).

15

Tert-Butyl 2-(4-bromo-1-oxoindolin-2-yl)-4-carbamoylbutanoate

Triethylamine (4.66 g, 46.09 mmol) was added to a stirred suspension of methyl 3-bromo-2-bromomethylbenzoate (6.45 g, 20.95 mmol) and L-glutamine t-butyl ester hydrochloride (5.0 g, 20.95 mmol) in THF (100 mL). The mixture was heated to reflux for 18 hours. The 20 mixture was cooled to room temperature and solvent was removed. The residue was dissolved in methylene chloride (100 mL) and washed with water (2x80 mL), brine (80 mL) and dried (MgSO_4). Solvent was removed and the residue was purified by chromatography (CH_2Cl_2 : CH_3OH 97.5:2.5) to afford tert-butyl 2-(4-bromo-1-oxoindolin-2-yl)-4-carbamoylbutanoate (3.97 g, 48%): $^1\text{H NMR}$ (CDCl_3) δ 7.74 (d, $J=7.1$ Hz, 1H), 7.65 (d, $J=7.9$ Hz, 1H), 7.35 (t, $J=7.8$ Hz, 1H), 6.15 (s, 1H), 5.77 (s, 1H), 5.02-4.96 (m, 1H), 4.58 (d, $J=17.4$ Hz, 1H), 4.34 (d, $J=17.4$ Hz, 1H), 2.45-2.10 (m, 4H), 1.46 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3) δ 173.83, 169.42, 168.74, 142.28, 134.70, 133.65, 129.80, 122.70, 117.75, 82.66, 54.29, 47.80, 32.27, 27.95, 25.54.

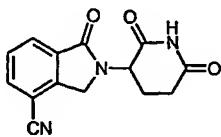
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Tert-Butyl 2-(4-cyano-1-oxoindolin-2-yl)-4-carbamoylbutanoate

A mixture of tert-butyl 2-(4-bromo-1-oxoindolin-2-yl)-4-carbamoylbutanoate (1.2 g, 3.02 mmol), zinc cyanide (0.21 g, 1.81 mmol), tris(dibenzylideneacetone)dipalladium (0.06g, 0.06 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.067 g, 0.12 mmol) in deoxygenated DMF (15 mL) was heated to 120°C under N_2 for 6 hours. The mixture was cooled to room 35 temperature and poured into EtOAc (100 mL) and sat. NaHCO_3 (40 mL). The EtOAc

- solution was washed with water (2x40 mL), brine (40 mL), and dried (MgSO_4). Solvent was removed and the residue was purified by chromatography (CH_2Cl_2 : CH_3OH 97.5:2.5) to afford tert-butyl 2-(4-cyano-1-oxoisoindolin-2-yl)-4-carbamoylbutanoate (0.77 g, 74%): ^1H NMR (CDCl_3) δ 8.07-8.03 (dd, $J=0.7$ and 7.4 Hz, 1H), 7.86-7.83 (dd, $J=1.0$ and 7.9 Hz, 1H), 7.61 (t, $J=7.6$ Hz, 1H), 5.91 (s, 1H), 5.68 (s, 1H), 5.03-4.98 (m, 1H), 4.85 (d, $J=17.9$ Hz, 1H), 4.62 (d, $J=17.9$ Hz, 1H), 2.48-2.41(m, 4H), 1.46 (s, 9H); ^{13}C NMR (CDCl_3) δ 173.56, 169.21, 167.70, 145.23, 134.94, 133.11, 128.93, 128.21, 115.65, 107.86, 82.98, 63.68, 54.47, 46.55, 32.34, 27.95, 25.46.
- 5 2-(4-Cyano-1-oxoisoindolin-2-yl)-4-carbamoylbutanoic acid
A mixture of tert-butyl 2-(4-cyano-1-oxoisoindolin-2-yl)-4-carbamoylbutanoate (1.0 g, 2.91 mmol) and trifluoroacetic acid (5 mL) was stirred for 2 hours. The mixture was concentrated and the residue was crystallized from ether (15 mL) to give 2-(4-cyano-1-oxoisoindolin-2-yl)-4-carbamoylbutanoic acid (0.74 g, 89%) as a white solid: ^1H NMR
15 (DMSO-d₆) δ 13.12 (b, 1H), 8.12 (d, $J=7.6$ Hz, 1H), 8.03 (d, $J=7.6$ Hz, 1H), 7.73 (t, $J=7.6$ Hz, 1H), 7.23 (s, 1H), 6.76 (s, 1H), 4.80-4.62 (m, 3H), 2.32-2.09 (m, 4H).

2-(2,6-Dioxo(3-piperidyl))-1-oxoisoindoline-4-carbonitrile

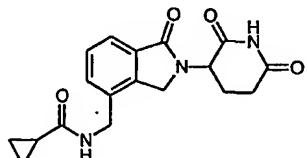
- 20 
- A mixture of 2-(4-cyano-1-oxoisoindolin-2-yl)-4carbamoylbutanoic acid (0.6 g, 2.09 mmol)
25 and 1,1-carbonyldiimidazole (0.44 g, 2.72 mmol) in acetonitrile (20 mL) was heated to reflux for 2 hours. The mixture was cooled to room temperature and filtered to give 2-(2,6-dioxo(3-piperidyl))-1-oxoisoindoline-4-carbonitrile (0.44 g, 83%) as a white solid: mp 312-314°C; ^1H NMR (DMSO-d₆) δ 11.04 (s, 1H), 8.16 (d, $J=7.0$ Hz, 1H), 8.06 (d, $J=7.1$ Hz, 1H), 7.74 (t, $J=7.7$ Hz, 1H), 5.20-5.13 (dd, $J=5.2$ and 13.2 Hz, 1H), 4.69 (d, $J=18.1$ Hz, 1H),
30 4.57 (d, $J=18.1$ Hz, 1H), 2.97-2.85 (m, 1H), 2.64-2.45 (m, 2H); 2.05-1.97 (m, 1H); ^{13}C NMR (DMSO-d₆) δ 172.81, 170.69, 166.49, 145.36, 135.37, 132.85, 129.36, 127.91, 116.01, 107.09, 51.77, 46.72, 31.14, 22.22; Anal. Calcd. For C₁₄H₁₁N₃O₃: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.26; H, 4.10; N, 15.51.
- 35 3-[4-(Aminomethyl)-1-oxoisoindolin-2-yl]piperidine-2,6-dione Hydrochloride

A mixture of 2-(2,6-dioxo(3-piperidyl))-1-oxoisooindoline-4-carbonitrile (1.0 g, 3.71 mmol) and 10% Pd/C (0.2 g) in 4N HCl (20 mL) and methanol (600 mL) was hydrogenated at 50 psi for 17 hours. The mixture was filtered through celite and the filtrate was concentrated. The residue was stirred with ether (30 mL) to give 3-[4-(aminomethyl)-1-oxoisooindolin-2-yl]piperidine-2,6-dione hydrochloride (1.1 g, 99%) as a white solid: ¹H NMR (DMSO-d₆) δ 11.06 (s, 1H), 8.64 (s, 3H), 7.79 (d, J=7.5 Hz, 1H), 7.74 (d, J=7.4 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 5.21-5.14 (dd, J=5.0 and 13.2 Hz, 1H), 4.69 (d, J=17.4 Hz, 1H), 4.51 (d, J=17.4 Hz, 1H), 4.09 (d, J=4.9 Hz, 2H), 3.00-2.87 (m, 1H), 2.66-2.35 (m, 2H), 2.03-1.98 (m, 1H); ¹³C NMR (DMSO-d₆) δ 172.87, 170.92, 167.77, 141.58, 132.50, 131.88, 129.39, 128.48, 123.25, 51.52, 46.19, 38.39, 31.17, 22.69.

N-{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisooindolin-4-yl]methyl}cyclopropylcarboxamide

I-140

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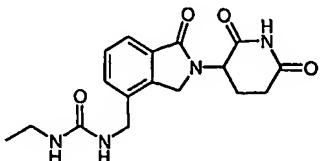


1,8-Diazabicyclo[5.4.0]undec-7-ene (0.7 g, 4.62 mmol) was added to a stirred suspension of 20 3-[4-(aminomethyl)-1-oxoisooindolin-2-yl]piperidine-2,6-dione hydrochloride (0.65 g, 2.10 mmol) in acetonitrile (50 mL). After stirring for 30 min, cyclopropanecarbonyl chloride (0.24 g, 2.31 mmol) was added. The mixture was stirred at room temperature for 17 hours. The mixture was filtered and the solid was recrystallized from methanol (100 mL) to afford 25 N-{[2-(2,6-dioxo(3-piperidyl))-1-oxoisooindolin-4-yl]methyl}cyclopropylcarboxamide (0.36 g, 50%) as a white solid: mp 262-264°C; ¹H NMR (DMSO-d₆) δ 11.02 (s, 1H), 8.63 (t, J=5.7 Hz, 1H), 7.65-7.47 (m, 3H), 5.18-5.11 (dd, J=5.0 and 13.2 Hz, 1H), 4.46 (d, J=17.3 Hz, 1H), 4.38-4.31 (m, 3H), 3.00-2.85 (m, 1H), 2.65-2.30 (m, 2H), 2.04-1.99 (m, 1H), 1.64-1.54 (m, 1H), 0.69-0.65 (m, 4H); ¹³C NMR (DMSO-d₆) δ 172.82, 172.69, 170.96, 168.03, 140.08, 134.76, 131.66, 130.70, 128.30, 121.64, 51.54, 46.15, 31.16, 22.59, 13.47, 6.27; 30 Anal. Calcd. For C₁₈H₁₉N₃O₄: C, 63.33; H, 5.61; N, 12.31. Found: C, 62.97; H, 5.55; N, 12.33.

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N-{{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisindolin-4-yl]methyl}(ethylamino)carboxamide
I-141

5



1,8-Diazabicyclo[5.4.0]undec-7-ene (0.44 g, 2.91 mmol) was added to a stirred suspension of 3-[4-(aminomethyl)-1-oxoisindolin-2-yl]piperidine-2,6-dione hydrochloride (0.6 g, 1.94 mmol) in acetonitrile (50 mL). After stirring for 30 min, ethyl isocyanate (0.21 g, 2.91 mmol) was added. The mixture was stirred at room temperature for 17 hours. Solvent was removed and the residue was stirred with methylene chloride (70 mL) to give N-{{[2-(2,6-dioxo(3-piperidyl))-1-oxoisindolin-4-yl]methyl}(ethylamino)carboxamide (0.28 g, 42%) as a white solid: mp 341-343°C; ¹H NMR (DMSO-d₆) δ 11.02 (s, 1H), 7.62-7.47 (m, 3H), 6.40 (t, J=5.9 Hz, 1H), 5.95 (t, J=5.6 Hz, 1H), 5.18-5.10 (dd, J=5.3 and 13.3 Hz, 1H), 4.52-4.30 (dd, J=17.3 and 37.7 Hz, 2H), 4.28 (d, J=5.9 Hz, 2H), 3.04 (q, J=7.2 Hz, 2H), 3.01-2.86 (m, 1H), 2.65-2.34 (m, 2H), 2.04-1.99 (m, 1H), 0.98 (t, J=7.2 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 172.82, 170.97, 168.10, 157.86, 139.78, 136.24, 131.55, 130.25, 128.16, 121.32, 51.51, 46.13, 34.14, 31.16, 22.59, 15.67; Anal. Calcd for C₁₇H₂₀N₄O₄: C, 59.29; H, 5.85; N, 16.27.
 20 Found: C, 58.98; H, 5.85; N, 16.89.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention.
 25 Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the appended claims.

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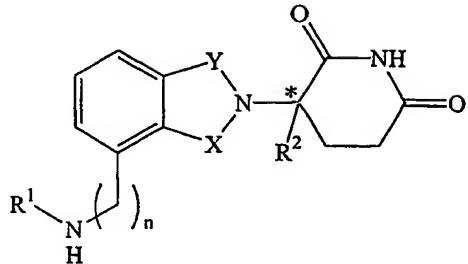
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What is claimed is:

1. A compound of the formula:

5

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or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

15

one of X and Y is C=O and the other is CH₂ or C=O;

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³,
20 C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³, C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

R² is H, F, benzyl, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, or (C₂-C₈)alkynyl;

25 R³ and R^{3'} are independently (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)QR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵;

30 R⁴ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₄)alkyl-OR⁵, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, or (C₀-C₄)alkyl-(C₂-C₅)heteroaryl;

R⁵ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, or (C₂-C₅)heteroaryl;

35

each occurrence of R⁶ is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₂-C₅)heteroaryl, or (C₀-C₈)alkyl-C(O)O-R⁵ or the R⁶ groups can join to form a heterocycloalkyl group;

- 5 n is 0 or 1; and the * represents a chiral-carbon center; with the proviso that when n is 0 then R¹ is not H.

2. The compound of claim 1, wherein the compound is the R-enantiomer or substantially R.

10

3. The compound of claim 1, wherein the compound is the S-enantiomer or substantially S.

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4. The compound of claim 1, wherein the compound is a racemic mixture.

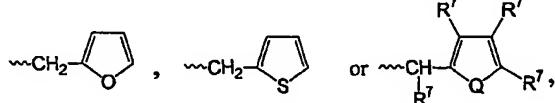
5. The compound of claim 1, wherein the enantiomeric excess is about 90% ee or more.

20

6. A compound of claim 1, wherein R² is H or (C₁-C₄)alkyl.

7. A compound of claim 1, wherein R¹ is H, (C₁-C₄)alkyl, CH₂OCH₃, CH₂CH₂OCH₃, or

25



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

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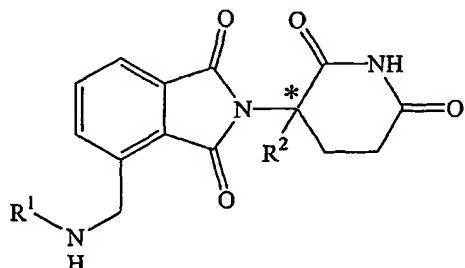
8. A compound of claim 1, wherein R¹ is C(O)R³.

9. A compound of claim 1, wherein R¹ is C(O)OR⁴.

5

10. The compound of claim 1 having the formula:

10



15 or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³, 20 C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³, C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

R² is H or (C₁-C₈)alkyl;

25 R³ and R³ are independently (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵;

30 R⁴ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₄)alkyl-OR⁵, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, or (C₀-C₄)alkyl-(C₂-C₅)heteroaryl;

R⁵ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, or (C₂-C₅)heteroaryl;

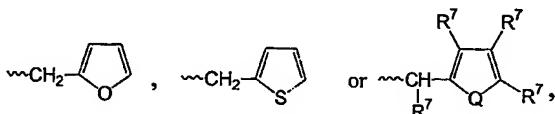
35

each occurrence of R⁶ is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₂-C₅)heteroaryl, or (C₀-C₈)alkyl-C(O)O-R⁵ or the R⁶ groups can join to form a heterocycloalkyl group; and

5 the * represents a chiral-carbon center.

11. A compound of claim 10, wherein R¹ is H, (C₁-C₄)alkyl, CH₂OCH₃, CH₂CH₂OCH₃, or

10



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen, 15 (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

20

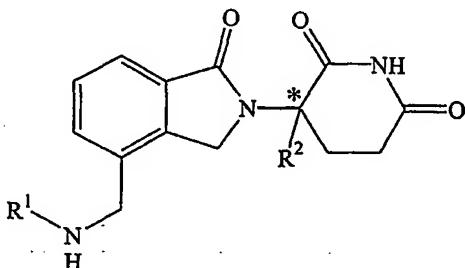
12. A compound of claim 10, wherein R¹ is C(O)R³.

13. A compound of claim 10, wherein R¹ is C(O)OR⁴.

14. The compound of claim 1 having the formula:

25

30



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

35

R^1 is H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^3'$, $C(S)NR^3R^3'$ or (C_1-C_8) alkyl- $O(CO)R^5$;

5

R^2 is H or (C_1-C_8) alkyl;

R^3 and R^3' are independently (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl,

10 (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_0-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$;

R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl- OR^5 , benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, or (C_0-C_4) alkyl- (C_2-C_5) heteroaryl;

15

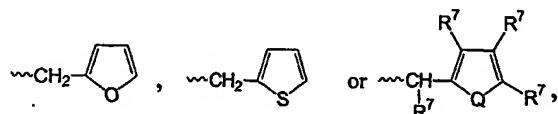
R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl;

each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl- $C(O)O-R^5$ or the R^6 groups can join to

20 form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

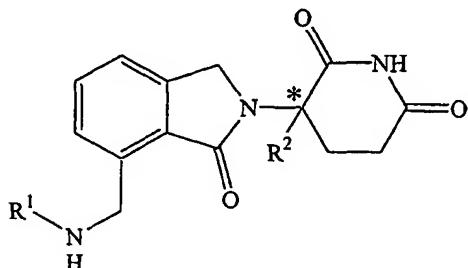
15. A compound of claim 14, wherein R^1 is H, (C_1-C_4) alkyl, CH_2OCH_3 ,
25 $CH_2CH_2OCH_3$, or



30 wherein Q is O or S, and each occurrence of R^7 is independently H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, halogen, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_0-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl
35 ring.

16. A compound of claim 14, wherein R¹ is C(O)R³.
17. A compound of claim 14, wherein R¹ is C(O)OR⁴.
- 5 18. A compound of claim 1 having the formula:

10



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer,
15 racemate, or mixture of stereoisomers thereof, wherein:

R¹ is H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl,
(C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, C(O)R³, C(S)R³,
C(O)OR⁴, (C₁–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, C(O)NHR³,
20 C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁–C₈)alkyl–O(CO)R⁵;

R² is H or (C₁–C₈)alkyl;

R³ and R^{3'} are independently (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl,
25 (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl,
(C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵,
(C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;

R⁴ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, (C₁–C₄)alkyl–OR⁵, benzyl, aryl,
30 (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, or (C₀–C₄)alkyl–(C₂–C₅)heteroaryl;

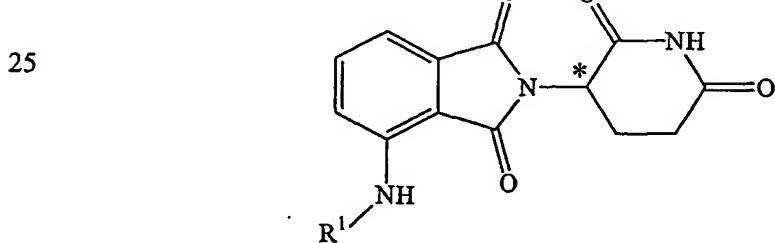
R⁵ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, or (C₂–C₅)heteroaryl;

each occurrence of R⁶ is independently H, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl,
35 benzyl, aryl, (C₂–C₅)heteroaryl, or (C₀–C₈)alkyl–C(O)O–R⁵ or the R⁶ groups can join to
form a heterocycloalkyl group; and

the * represents a chiral-carbon center.

19. A compound of claim 18, wherein R¹ is H, (C₁-C₄)alkyl, CH₂OCH₃, CH₂CH₂OCH₃ or
- 5
- The first structure is a methylene group connected to a furan ring. The second structure is a methylene group connected to a thiophene ring. The third structure is a cyclohexadiene ring with substituents R⁷ at positions 2 and 6, and Q at position 4.
- 10 wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, halogen, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl 15 ring.

- 15 20. A compound of claim 18, wherein R¹ is C(O)R³.
21. A compound of claim 18, wherein R¹ is C(O)OR⁴.
- 20 22. A compound of claim 1 having the formula:



- 30 30 or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³, C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³, C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

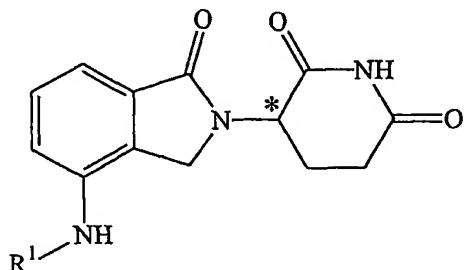
- R³ and R^{3'} are independently (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵,
- 5 (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵;
- R⁴ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, (C₁–C₄)alkyl–OR⁵, benzyl, aryl, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, or (C₀–C₄)alkyl–(C₂–C₅)heteroaryl;
- 10 R⁵ is (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, or (C₂–C₅)heteroaryl; each occurrence of R⁶ is independently H, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, (C₂–C₅)heteroaryl, or (C₀–C₈)alkyl–C(O)O–R⁵ or the R⁶ groups can join to form a heterocycloalkyl group; and
- 15 the * represents a chiral-carbon center.
23. A compound of claim 22, wherein R¹ is (C₁–C₈)alkyl, benzyl, CH₂OCH₃, CH₂CH₂OCH₃, or
- 20
-
- 25 wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, halogen, (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.
- 30
24. A compound of claim 22, wherein R¹ is C(O)R³.
25. A compound of claim 24, wherein R³ is (C₀–C₄)alkyl–(C₂–C₅)heteroaryl,
- 35 (C₁–C₈)alkyl, aryl, or (C₀–C₄)alkyl–OR⁵.

26. A compound of claim 25, wherein heteroaryl is pyridyl, furyl, or thienyl.

27. A compound of claim 22, wherein R¹ is C(O)OR⁴.

5 28. A compound of claim 1 having the formula:

10



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer,
15 racemate, or mixture of stereoisomers thereof, wherein:

R¹ is H, (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl,
(C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, C(O)R³, C(S)R³,
C(O)OR⁴, (C₁-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵, (C₁-C₈)alkyl-C(O)OR⁵, C(O)NHR³,
20 C(S)NHR³, C(O)NR³R³, C(S)NR³R³ or (C₁-C₈)alkyl-O(CO)R⁵;

R³ and R³ are independently (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₂-C₈)alkenyl,
(C₂-C₈)alkynyl, benzyl, aryl, (C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl,
(C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₀-C₈)alkyl-N(R⁶)₂, (C₁-C₈)alkyl-OR⁵,
25 (C₁-C₈)alkyl-C(O)OR⁵, (C₁-C₈)alkyl-O(CO)R⁵, or C(O)OR⁵;

R⁴ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₄)alkyl-OR⁵, benzyl, aryl,
(C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, or (C₀-C₄)alkyl-(C₂-C₅)heteroaryl;

30 R⁵ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl, or (C₂-C₅)heteroaryl;

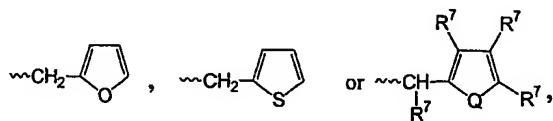
each occurrence of R⁶ is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
benzyl, aryl, (C₂-C₅)heteroaryl, or (C₀-C₈)alkyl-C(O)O-R⁵ or the R⁶ groups can join to
form a heterocycloalkyl group; and

35

the * represents a chiral-carbon center.

29. A compound of claim 28, wherein R¹ is (C₁–C₈)alkyl, benzyl, CH₂OCH₃, CH₂CH₂OCH₃, or

5



wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁–C₈)alkyl, (C₃–C₇)cycloalkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl, benzyl, aryl, halogen,
 10 (C₀–C₄)alkyl–(C₁–C₆)heterocycloalkyl, (C₀–C₄)alkyl–(C₂–C₅)heteroaryl,
 (C₀–C₈)alkyl–N(R⁶)₂, (C₁–C₈)alkyl–OR⁵, (C₁–C₈)alkyl–C(O)OR⁵, (C₁–C₈)alkyl–O(CO)R⁵, or
 C(O)OR⁵, or adjacent occurrences of R⁷ can be taken together to form a bicyclic alkyl or aryl ring.

15

30. A compound of claim 28, wherein R¹ is C(O)R³.

31. A compound of claim 30, wherein R³ is (C₀–C₄)alkyl–(C₂–C₅)heteroaryl, (C₁–C₈)alkyl, aryl, or (C₀–C₄)alkyl–OR⁵.

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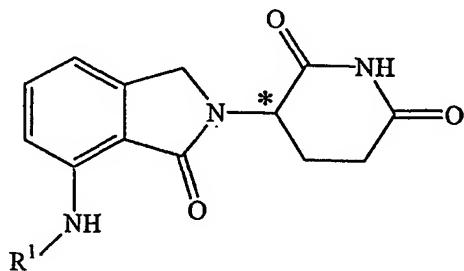
32. A compound of claim 31, wherein heteroaryl is pyridyl, furyl, or thienyl.

33. A compound of claim 28, wherein R¹ is C(O)OR⁴.

34. A compound of claim 1 having the formula:

25

30



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers thereof, wherein:

35

R^1 is H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl-(C_1-C_6)heterocycloalkyl, (C_0-C_4) alkyl-(C_2-C_5)heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl-N(R^6)₂, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl-C(O)OR⁵, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^3$, $C(S)NR^3R^3$ or (C_1-C_8) alkyl-O(CO)R⁵;

5

R^3 and R^3 are independently (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl-(C_1-C_6)heterocycloalkyl, (C_0-C_4) alkyl-(C_2-C_5)heteroaryl, (C_0-C_8) alkyl-N(R^6)₂, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl-C(O)OR⁵, (C_1-C_8) alkyl-O(CO)R⁵, or C(O)OR⁵;

10

R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl- OR^5 , benzyl, aryl, (C_0-C_4) alkyl-(C_1-C_6)heterocycloalkyl, or (C_0-C_4) alkyl-(C_2-C_5)heteroaryl;

R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl;

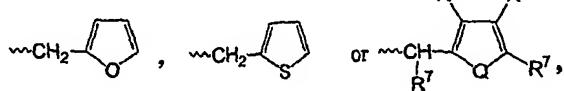
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each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl-C(O)O-R⁵ or the R^6 groups can join to form a heterocycloalkyl group; and

20 the * represents a chiral-carbon center.

35. A compound of claim 34, wherein R^1 is (C_1-C_8) alkyl, benzyl, CH_2OCH_3 , $CH_2CH_2OCH_3$, or

25



wherein Q is O or S, and each occurrence of R^7 is independently H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, halogen, 30 (C_0-C_4) alkyl-(C_1-C_6)heterocycloalkyl, (C_0-C_4) alkyl-(C_2-C_5)heteroaryl, (C_0-C_8) alkyl-N(R^6)₂, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl-C(O)OR⁵, (C_1-C_8) alkyl-O(CO)R⁵, or C(O)OR⁵, or adjacent occurrences of R^7 can be taken together to form a bicyclic alkyl or aryl ring.

35

36. A compound of claim 34, wherein R^1 is $C(O)R^3$.

37. A compound of claim 36, wherein R³ is (C₀—C₄)alkyl—(C₂—C₅)heteroaryl, (C₁—C₈)alkyl, aryl, or (C₀—C₄)alkyl—OR⁵.
38. A compound of claim 37, wherein heteroaryl is pyridyl, furyl, or thienyl.
- 5 39. A compound of claim 34, wherein R¹ is C(O)OR⁴.
40. A compound of claim 1 having the formula:
- 10 I-1 (2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid *tert*-butyl ester;
- I-2 4-(aminomethyl)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione;
- 15 I-3 N-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethy l)-acetamide;
- I-4 N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl}cyclopropyl-carboxamide;
- 20 I-5 (2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid ethyl ester;
- I-6 2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-ylmethyl)-carbamic acid benzyl ester;
- 25 I-7 2-chloro-N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl}acetamide;
- I-8 2-(dimethylamino)-N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl}-acetamide;
- 30 I-9 1-*tert*-butyl-3-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoind ol-4-ylmethyl)-urea;
- I-10 N-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl)methyl}-3,3-dimethylbutanamide;

- I-11 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-3-pyridylcarboxamide;
- I-12 3-{1-oxo-4-(benzylamino)isoindolin-2-yl}piperidine-2,6-dione;
- 5 I-13 2-(2,6-dioxo(3-piperidyl))-4-(benzylamino)isoindoline-1,3-dione;
- I-14 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}propanamide;
- 10 I-15 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}-3-pyridylcarboxamide;
- I-16 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}heptanamide;
- 15 I-17 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}-2-furylcarboxamide;
- 20 I-18 2-azido-*N*-(2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl-methyl)-acetamide;
- I-19 2-amino-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}acetamide;
- 25 I-20 ethyl 6-(*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}carbamoyl)hexanoate;
- I-21 3-((*tert*-butoxy)carbonylamino)-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}propanamide;
- 30 I-22 3-amino-*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}propanamide;
- I-23 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}-2-thienylcarboxamide;

- I-24 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl}-2-methoxyacetamide;
- 5 I-25 (*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl} carbamoyl)methyl acetate;
- I-26 ethyl 2-((*N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl} carbamoyl) amino)acetate;
- 10 I-27 *N*-{(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)methyl} (ethylamino)carboxamide;
- I-28 2-(2,6-Dioxo(3-piperidyl))-4-[(2-furylmethyl)amino]isoindoline-1,3-dione
- 15 I-29 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-methoxyacetamide;
- I-30 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)heptanamide;
- 20 I-31 {*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)carbamoyl} methyl acetate;
- I-32 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)pentanamide;
- 25 I-33 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-thienylcarboxamide;
- I-34 methyl {*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)carbamoyl} formate;
- 30 I-35 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-furylcarboxamide;
- I-36 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)benzamide;
- 35 I-37 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)propanamide;

- I-38 methyl 3-{*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)carbamoyl}propanoate;
- I-39 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-phenylacetamide;
- I-40 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-pyridylcarboxamide;
- I-41 *N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)-2-chloroacetamide;
- I-42 2-azido-*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)acetamide;
- I-43 2-amino-*N*-(2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl)acetamide;
- I-44 *N*-(2-(2,6-dioxo(3-piperidyl))-1-oxoisooindolin-4-yl)-2-chloroacetamide;
- I-45 2-azido-*N*-(2-(2,6-dioxo(3-piperidyl))-1-oxoisooindolin-4-yl)acetamide;
- I-46 2-amino-*N*-(2-(2,6-dioxo(3-piperidyl))-1-oxoisooindolin-4-yl)acetamide;
- I-47 3-{4-((2-furylmethyl)amino)-1-oxoisooindolin-2-yl}piperidine-2,6-dione; or
- I-48 3-(1-oxo-4-(pentylamino)isoindolin-2-yl)piperidine-2,6-dione;
- I-49 2-(2,6-dioxo-piperidin-3-yl)-4-(2-methoxy-ethylamino)-isoindole-1,3-dione;
- I-50 2-benzyloxy-*N*-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;
- I-51 2-(2,6-dioxo-piperidin-3-yl)-4-pentylamino-isoindole-1,3-dione;
- I-52 3-chloro-*N*-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;
- I-53 *N*-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-phenoxy-acetamide;

- I-54 4-(2-benzyloxy-ethylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;
- 5 I-55 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-fluoro-benzamide;
- I-56 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methyl-benzamide;
- 10 I-57 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-benzamide;
- I-58 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-trifluoromethyl-benzamide;
- 15 I-59 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-nitro-benzamide;
- 20 I-60 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-butyramide;
- I-61 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylamino-acetamide;
- 25 I-62 2-(2,6-dioxo-piperidin-3-yl)-4-heptylamino-isoindole-1,3-dione;
- I-63 4-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;
- 30 I-64 cyclopropanecarboxylic acid [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-amide;
- I-65 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-fluoro-benzamide;
- 35

- I-66 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-trifluoromethyl-benzamide;
- 5 I-67 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methyl-benzamide;
- I-68 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-nitro-benzamide;
- 10 I-69 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-ethoxy-acetamide;
- I-70 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methylsulfanyl-acetamide;
- 15 I-71 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methoxy-benzamide;
- I-72 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-fluoro-benzamide;
- 20 I-73 7-amino-N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}heptanamide;
- I-74 N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}butanamide;
- I-75 N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}benzamide;
- I-76 N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}phenylacetamide;
- 30 I-77 N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-pyridylcarboxamide;
- I-78 N-{{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}undecamide;

- I-79 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}-2-methylpropanamide;
- I-80 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclopentylcarboxamide; 5
- I-81 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}cyclohexylcarboxamide;
- I-82 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(phenylamino)carboxamide; 10
- I-83 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(butylamino)carboxamide; 15
- I-84 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(propylamino)carboxamide;
- I-85 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclohexylamino)carboxamide ; 20
- I-86 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}[(methylethylamino)]carboxamide;
- I-87 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(octylamino)carboxamide; 25
- I-88 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(benzylamino)carboxamide; 30
- I-89 N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclopropylamino)carboxamide;
- I-90 2-chloro-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-35 1H-isooindol-4-yl]-benzamide;

- I-91 [2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-carbamic acid benzyl ester;
- I-92 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;
- I-93 Pentanoic acid [2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-amide;
- I-94 N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-propionamide;
- I-95 N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-nicotinamide;
- I-96 2-(2,6-dioxo-piperidin-3-yl)-4-{{[(furan-2-ylmethyl)-amino]-methyl}}-isoindole-1,3-dione;
- I-97 N-[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-benzamide;
- I-98 2-dimethylamino-N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-acetamide;
- I-99 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-methyl-benzamide;
- I-100 Heptanoic acid[2-(2,6-dioxo-piperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-4-yl]-dihydro-1H-isoindol-4-yl]-amide;
- I-101 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3,3-dimethyl-butyramide;
- I-102 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-isobutyramide;

- I-103 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-phenyl-propionamide;
- I-104 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-4-methoxy-benzamide
- I-105 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-trifluoromethyl-benzamide;
- I-106 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-malonamic acid methyl ester;
- I-107 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-3-methoxy-propionamide;
- I-108 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]-2-hydroxy-acetamide
- I-109 4-[(furan-2-ylmethyl)-amino]-2-(1-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;
- I-110 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-isonicotinamide;
- I-111 N-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-acetamide;
- I-112 {5-[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylcarbamoyl]-pentyl}-carbamic acid benzyl ester;
- I-113 2-(2,6-Dioxo(3-piperidyl))-4-({[(cyclohexylamino)thioxomethyl]amino} methyl)isoindole -1,3-dione;
- I-114 2-(2,6-Dioxo(3-piperidyl))-4-({[(ethylamino)thioxomethyl]amino} methyl)isoindole -1,3-dione;

- I-115 2-(2,6-Dioxo(3-piperidyl))-4-({[(propylamino)thioxomethyl]amino} methyl)isoindole -1,3-dione;
- 5 I-116 N-[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisindolin-4-yl]-2-chlorobenzylamine;
- I-117 {5-[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-ylcarbamoyl]-pentyl}-carbamic acid benzyl ester;
- 10 I-118 2-Methoxy-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-acetamide;
- I-119 Pentanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-amide;
- 15 I-120 Heptanoic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-amide;
- I-121 3-Chloro-N-[2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-benzamide;
- 20 I-122 N-[2-(3-Methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-propionamide;
- I-123 Thiophene-2-carboxylic acid [2-(3-methyl-2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]-amide;
- 25 I-124 2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-methyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione;
- I-125 2-(2,6-Dioxo-piperidin-3-yl)-4-[(5-hydroxymethyl-furan-2-ylmethyl)-amino]-isoindole-1,3-dione;
- 30 I-126 2-(2,6-Dioxo-piperidin-3-yl)-4-[(thiophen-2-ylmethyl)-amino]-isoindole-1,3-dione;
- 35

- I-127 4-(3-Chloro-benzylamino)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;
- I-128 2-(2,6-Dioxo-piperidin-3-yl)-4-[(pyridin-3-ylmethyl)-amino]-isoindole-1,3-dione;
- 5 I-129 5-{[2-(2,6-Dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylamino]-methyl}-furan-2-carboxylic acid;
- I-130 4-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione ;
- 10 I-131 4-[(Benzofuran-2-ylmethyl)-amino]-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione ;
- I-132 4-(3-Chloro-benzylamino)-2-(3-methyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione;
- 15 I-133 3-[4-(3-Chloro-benzylamino)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione;
- 20 I-134 N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(cyclopentylamino)carboxamide;
- I-135 N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(3-pyridylamino)carboxamide Hydrochloride;
- 25 I-136 N-{[2,(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}piperidylcarboxamide;
- I-137 Tert-Butyl 4-(N-{[2-(2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(carbamoyl)piperazinecarboxylate;
- 30 I-138 N-{[2-(2,6-Dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}(diethylamino)carboxamide;
- 35

- I-139 Cyclopropyl-N-{[2-(3-methyl-2,6-dioxo(3-piperidyl))-1,3-dioxoisooindolin-4-yl]methyl}carboxamide;
- 5 I-140 N-{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisooindolin-4-yl]methyl}cyclopropylcarboxamide;
- I-141 N-{[2-(2,6-Dioxo(3-piperidyl))-1-oxoisooindolin-4-yl]methyl}(ethylamino)carboxamide; or
- 10 I-142 Piperazine-1-carboxylic acid
[2-(2,6-dioxo-piperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-ylmethyl]-amide
- or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer,
15 racemate, or mixture of stereoisomers thereof.
41. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 1 and a pharmaceutically acceptable vehicle or carrier.
- 20 42. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 10 and a pharmaceutically acceptable vehicle or carrier.
43. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 14 and a pharmaceutically acceptable vehicle or carrier.
- 25 44. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 18 and a pharmaceutically acceptable vehicle or carrier.
45. A pharmaceutical composition comprising a therapeutically effective amount
30 of a compound of claim 22 and a pharmaceutically acceptable vehicle or carrier.
46. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 28 and a pharmaceutically acceptable vehicle or carrier.
- 35 47. A pharmaceutical composition comprising a therapeutically effective amount
of a compound of claim 34 and a pharmaceutically acceptable vehicle or carrier.

48. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 40 and a pharmaceutically acceptable vehicle or carrier.

49. A method of modulating the production of TNF- α in a mammal comprising
5 administering to said mammal an effective amount of a compound of claim 1.

50. A method of modulating the production of IL-1 β in a mammal comprising
administering to said mammal an effective amount of a compound of claim 1.

10 51. A method of modulating the production of IL-10 in a mammal comprising
administering to said mammal an effective amount of a compound of claim 1.

52. A method of modulating the production of T-cells in a mammal comprising
administering to said mammal an effective amount of a compound of claim 1.

15 53. A method of treating cancer in a mammal, comprising administering to a
mammal in need thereof a therapeutically effective amount of a compound of claim 1, 10,
14, 18, 22, 28, 34, or 40.

20 54. The method of claim 53, wherein the cancer is a solid tumor or a blood born
tumor.

55. The method of claim 53, wherein the cancer is cancer of the skin, blood,
lymph node, breast, cervix, uterus, gastrointestinal tract, lung, ovary, prostate, mouth, brain,
25 head, neck, throat, colon, rectum, testes, kidney, pancreas, bone, spleen, liver, bladder,
larynx, or nasal passages.

56. The method of claim 53, wherein the cancer is melanoma, multiple
myeloma, or a leukemia.

30 57. A method of treating cancer in a mammal, comprising administering to a
mammal in need thereof a therapeutically effective amount of a compound of claim 1 and
another chemotherapeutic agent.

58. The method of claim 57, wherein the other cancer chemotherapeutic agent is paclitaxel, cisplatin, tamoxifen, docetaxel, epirubicin, doxorubicin, irinotecan, leuprolide, bicalutamide, goserelin implant, gemcitabine, or sargramostim.

5 59. The method of claim 57, wherein the other cancer chemotherapeutic agent is an anti-cancer vaccine.

60. A method of treating an inflammatory disorder in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a 10 compound of claim 1.

61. The method of claim 60, wherein the inflammatory disorder is arthritis, rheumatoid spondylitis, psoriasis, inflammatory bowel disease, post ischemic perfusion injury, or chronic inflammatory pulmonary disease.

15 62. The method of claim 61, wherein the arthritis is rheumatoid arthritis or osteoarthritis.

63. A method of treating heart disease in a mammal comprising administering to 20 a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

64. A method of modulating the production of TNF- α in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

25 65. A method of modulating the production of IL-1 β in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

66. A method of modulating the production of IL-10 in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

30 67. A method of modulating the production of T-cells in a mammalian cell or tissue comprising contacting an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/50401

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D401/04	C07D401/14	C07D407/14	C07D409/14	A61K31/445

A61K31/44 A61K31/495 A61P29/00 A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 46258 A (CHEN ROGER SHEN CHU ;MAN HON WAH (US); CELGENE CORP (US); MULLER G) 16 September 1999 (1999-09-16) Claims 1,9 the whole document ---	1-67
X	US 5 874 448 A (CHEN ROGER SHEN-CHU ET AL) 23 February 1999 (1999-02-23) Claims 1,9 the whole document ---	1-67
X	WO 98 54170 A (CHEN ROGER SHEN CHU ;CELGENE CORP (US); MULLER GEORGE W (US); STIR) 3 December 1998 (1998-12-03) Claim 6, ex. 12 the whole document ---	1-67

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

13/06/2002

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/50401

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03502 A (CHEN ROGER SHEN CHU ;CELGENE CORP (US); MULLER GEORGE W (US); STIR) 29 January 1998 (1998-01-29) Claim 1, ex. 15-17 the whole document ----	1-67
X	US 5 635 517 A (CHEN ROGER S-C ET AL) 3 June 1997 (1997-06-03) Ex. 1 the whole document ----	1-67
X	MULLER G W ET AL: "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 11, 7 June 1999 (1999-06-07), pages 1625-1630, XP004169632 ISSN: 0960-894X Compound 8a the whole document ----	1-67
X	MIYACHI H ET AL: "Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: Influence of substituents at the phthaloyl moiety on the activity and stereoselectivity" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 46, no. 7, July 1998 (1998-07), pages 1165-1168, XP002107774 ISSN: 0009-2363 Compound 9c the whole document ----	1-67

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/50401

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9946258	A	16-09-1999	US	5955476 A		21-09-1999
			AU	1413899 A		27-09-1999
			CA	2317834 A1		16-09-1999
			CN	1282330 T		31-01-2001
			EP	1062214 A1		27-12-2000
			FI	20001192 A		14-07-2000
			HU	0100615 A2		28-10-2001
			JP	2002506068 T		26-02-2002
			NO	20002529 A		30-06-2000
			NZ	504650 A		30-11-2001
			PL	340547 A1		12-02-2001
			SK	7382000 A3		11-12-2000
			TR	200002627 T2		21-11-2000
			WO	9946258 A1		16-09-1999
US 5874448	A	23-02-1999	FI	20001192 A		14-07-2000
			NO	20002529 A		30-06-2000
			SK	7382000 A3		11-12-2000
			US	5955476 A		21-09-1999
WO 9854170	A	03-12-1998	AU	715779 B2		10-02-2000
			AU	741982 B2		13-12-2001
			AU	7701298 A		30-12-1998
			CA	2261762 A1		29-01-1998
			CN	1239959 A		29-12-1999
			CN	1258293 T		28-06-2000
			CZ	9900202 A3		16-06-1999
			EP	0925294 A1		30-06-1999
			EP	0984955 A1		15-03-2000
			FI	990101 A		19-03-1999
			FI	992490 A		27-01-2000
			HU	0003217 A2		28-06-2001
			HU	9903929 A2		28-05-2000
			JP	2002501536 T		15-01-2002
			JP	2001503384 T		13-03-2001
			NO	995751 A		28-01-2000
			NZ	333903 A		28-02-2000
			NZ	501429 A		30-11-2001
			PL	332867 A1		25-10-1999
			PL	337124 A1		31-07-2000
			SK	9199 A3		12-07-1999
			SK	163099 A3		12-06-2000
			TR	200000107 T2		21-07-2000
			WO	9803502 A1		29-01-1998
			WO	9854170 A1		03-12-1998
			US	6281230 B1		28-08-2001
			US	6316471 B1		13-11-2001
			US	6335349 B1		01-01-2002
WO 9803502	A	29-01-1998	US	5635517 A		03-06-1997
			US	5798368 A		25-08-1998
			AU	715779 B2		10-02-2000
			AU	3899897 A		10-02-1998
			CA	2261762 A1		29-01-1998
			CN	1239959 A		29-12-1999
			CZ	9900202 A3		16-06-1999
			EP	0925294 A1		30-06-1999
			FI	990101 A		19-03-1999

Information on patent family members

International Application No

PCT/US 01/50401

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9803502	A		JP 2001503384 T NZ 333903 A PL 332867 A1 SK 9199 A3 WO 9803502 A1 US 6281230 B1 US 6316471 B1 US 6335349 B1 US 2002045643 A1 AU 741982 B2 AU 7701298 A CN 1258293 T EP 0984955 A1 FI 992490 A HU 0003217 A2 HU 9903929 A2 JP 2002501536 T NO 995751 A NZ 501429 A PL 337124 A1 SK 163099 A3 TR 200000107 T2 WO 9854170 A1	13-03-2001 28-02-2000 25-10-1999 12-07-1999 29-01-1998 28-08-2001 13-11-2001 01-01-2002 18-04-2002 13-12-2001 30-12-1998 28-06-2000 15-03-2000 27-01-2000 28-06-2001 28-05-2000 15-01-2002 28-01-2000 30-11-2001 31-07-2000 12-06-2000 21-07-2000 03-12-1998
US 5635517	A	03-06-1997	AU 715779 B2 AU 3899897 A CA 2261762 A1 CN 1239959 A CZ 9900202 A3 EP 0925294 A1 FI 990101 A JP 2001503384 T NZ 333903 A PL 332867 A1 SK 9199 A3 WO 9803502 A1 US 6281230 B1 US 6316471 B1 US 6335349 B1 US 2002045643 A1	10-02-2000 10-02-1998 29-01-1998 29-12-1999 16-06-1999 30-06-1999 19-03-1999 13-03-2001 28-02-2000 25-10-1999 12-07-1999 29-01-1998 28-08-2001 13-11-2001 01-01-2002 18-04-2002